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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

SEPTEMBER

1959

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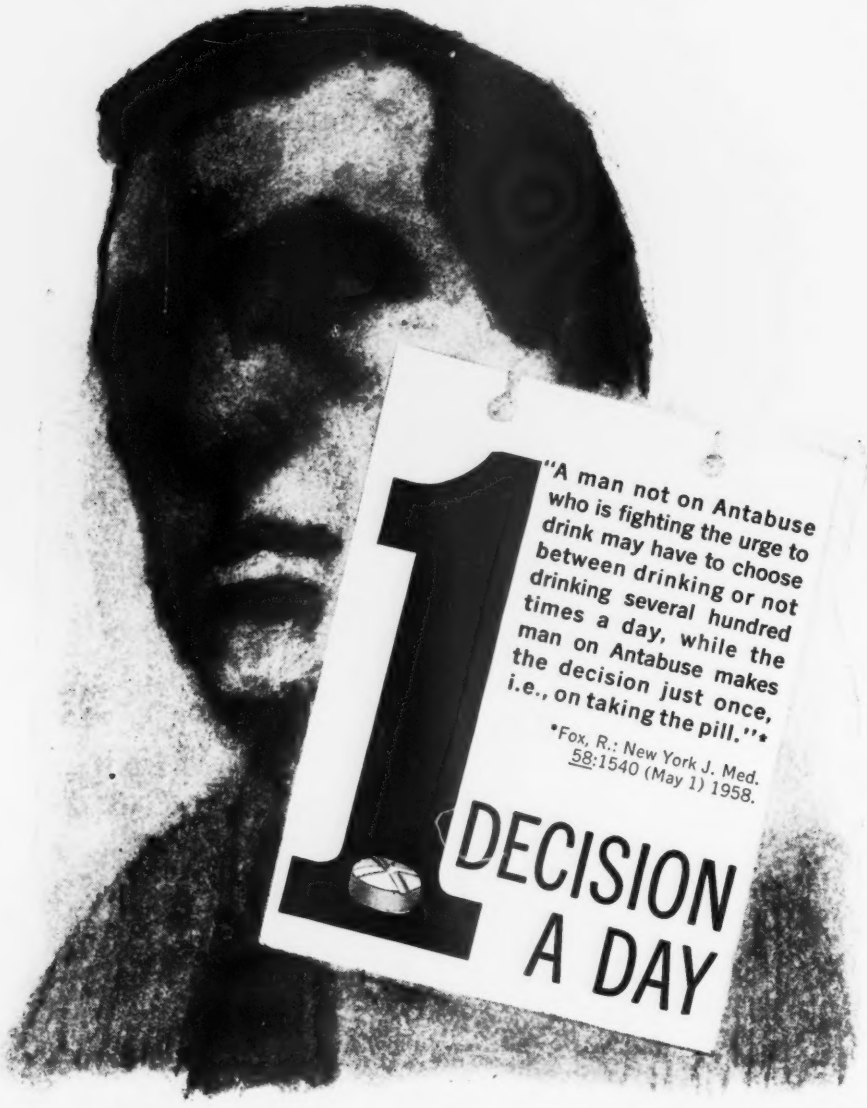
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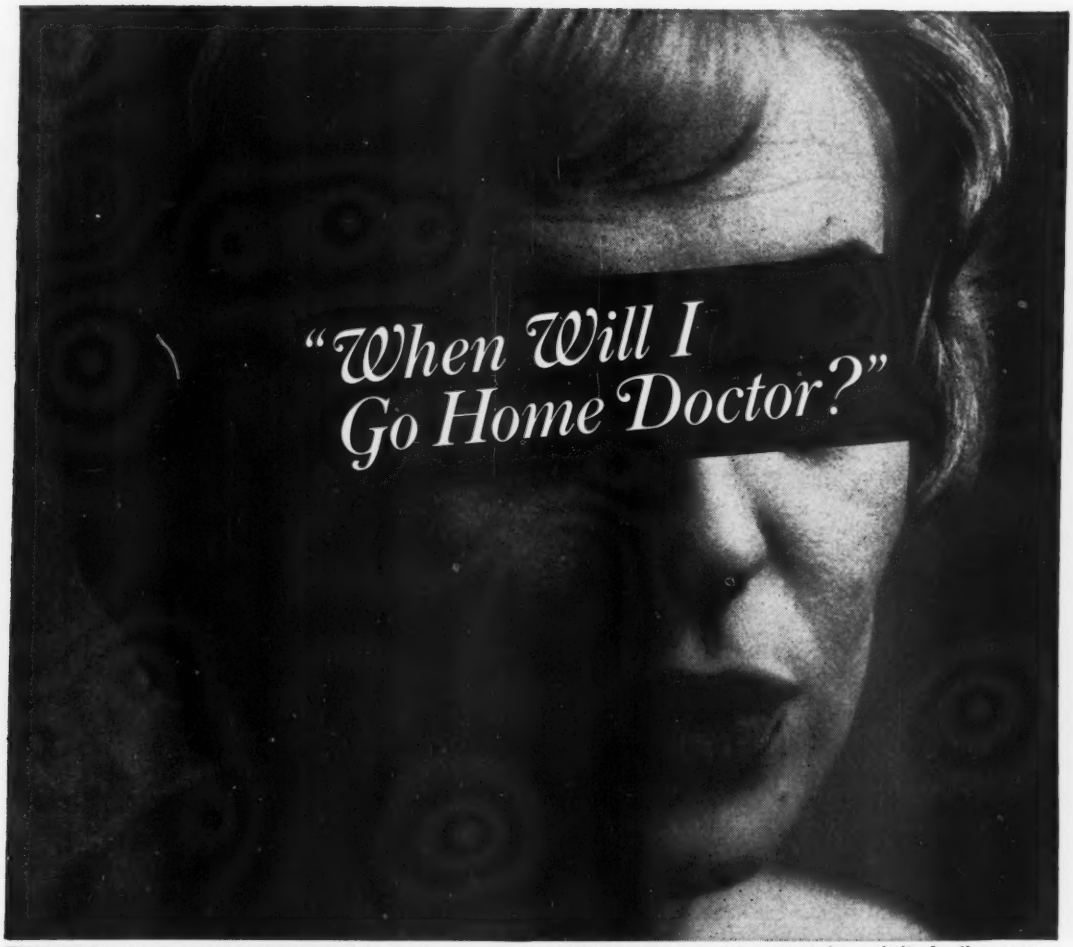

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4. Bruckman, N. S.; Saunders, J. C., and Kline, N. S.: Monographs on Therapy 3:24 (May) 1958.

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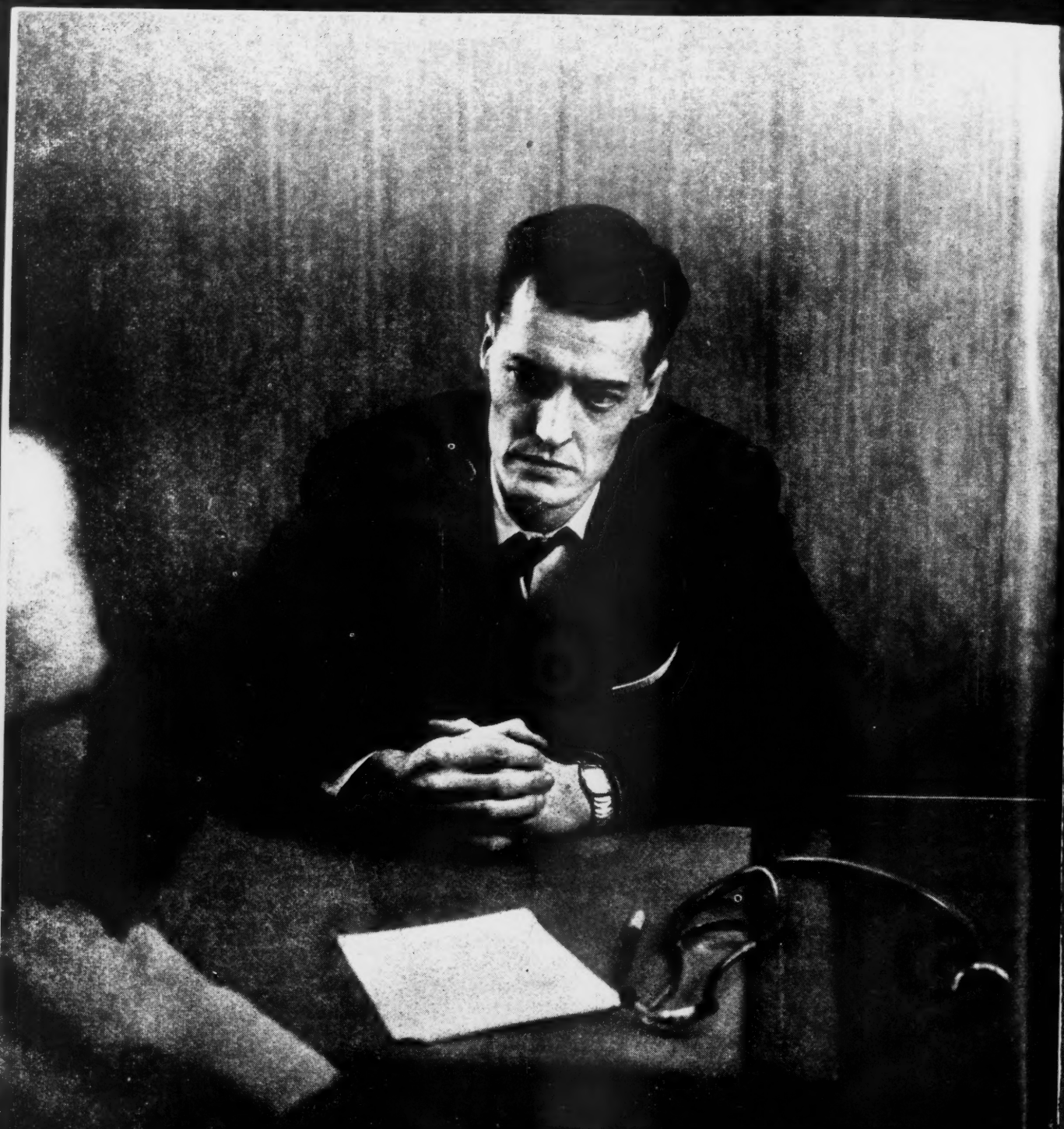

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References:
1. Pennington, V.M.: The use of Deprol in chronic psychotic patients. Am. J. Psychiat. 115:250, Sept. 1958. **2.** Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **3.** Settel, E.: Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Submitted for publication, 1958. **4.** Personal communications from physicians; in the files of Wallace Laboratories.

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DISEASES *of the* Nervous System

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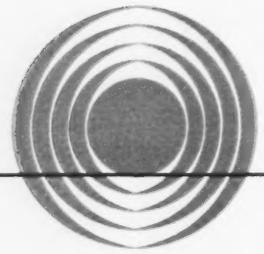

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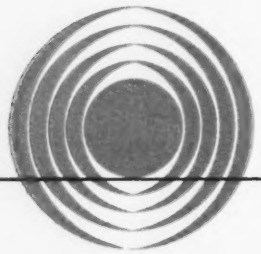

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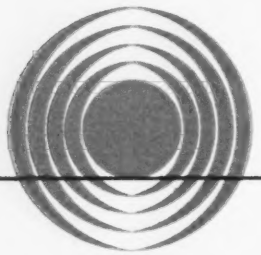

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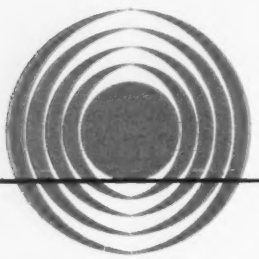

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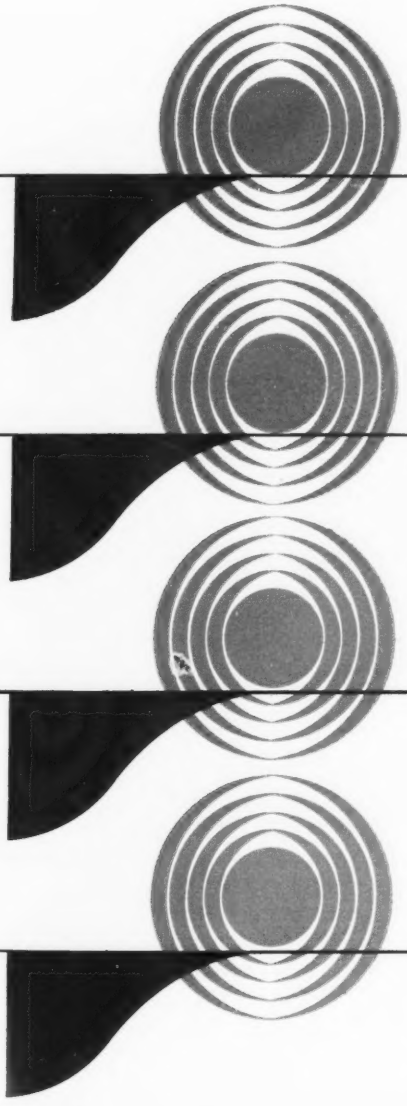

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Differential Response of Schizophrenic and Other Psychiatric Patients to Atropine

A. HOFFER, M.D., and M. J. CALLBECK, R.N.

Introduction

In earlier communications, Hoffer[1,2] (1954) reported that 3 mg. of atropine sulfate injected intramuscularly[1] lowered the systolic blood pressure of schizophrenic and epileptic patients in contrast to other psychiatric groups and[2] did not change the leukocyte counts in contrast to other groups in whom it induced changes similar to those found after injection of adrenaline. The systolic pressure response and the lack of change in leukocytes were used for developing a physiological score which discriminated between a group of schizophrenic patients from a group not schizophrenic, Hoffer[3] (1954).

Statistics must be interpreted with caution. Kline[5] (1958) properly has reminded psychiatric statisticians that when two groups of patients are examined for differences, these will be found by chance, i.e., if 20 variables are examined, one may show a significant difference between the groups. The significance of any variable must be checked by repeating the study on new groups of patients without using any of the data from the previous study, for when a significant difference is found which is due to chance it may by its weight show significance for the entire series as it is extended.

This criticism does not apply to the original atropine report because (1) it was predicted by the hypothesis that the sympathetic nervous system of schizophrenics was overly active and therefore under reactive, (2) it was the only variable used for the detection of difference. Nevertheless, it is imperative that chance be excluded. For this reason, the studies were continued both to test the conclusion of the earlier work and to measure the role of variables such as age, weight and sex which were previously neglected.

Materials and Method

The atropine test is described in our previous study.[1,2,3] Psychiatric patients from the Munroe Wing, General Hospital, Regina and the University Hospital, Saskatoon were tested. The test was given to 166 patients after the original reports had been completed. When we found that the results from this group confirmed the earlier reports, we added data from 105 patients from our previous study. The patients were examined for the presence of the Lewis and Piotrowski schizophrenia factors[6] slightly modified by Hoffer and Parsons.[4]

Testing was done by resident psychiatrists and by one of us (M.J.C.) before the clinical diagnosis was established. The diagnosis was made by the psychiatric staff of the two units. Where there was a disagreement in diagnosis between the clinical and research psychiatrists, the clinical diagnosis was used in this study. The patients are all being watched since discharge for changes in the clinical syndrome to determine whether neurotic patients who showed abnormal atropine reaction are in reality pseudoneurotic schizophrenics or whether neurotic patients can show a similar overly active sympathetic nervous system.

In this study, the blood pressure response to atropine was scored differently than in our original report. In the first report the

From University Hospital, Saskatoon, Sask., Canada.

Research supported by National Health Grants, Ottawa, and the Rockefeller Foundation, New York, under the auspices of the Saskatchewan Committee on Schizophrenia Research.

mean systolic pressure of the two blood pressure readings 25 and 30 minutes after the injection of atropine was compared to the mean of the last two readings just before it was given. For example if the mean of the last two readings was 125 mm of mercury and the baseline mean was 120 mm, the response was said to be normal. No provision was made for random error in these readings. In this study the same baseline was used. A line was drawn across the charting paper (100 squares per square inch) through the baseline. Perpendicular lines were dropped from the experimental systolic pressure curve to the baseline at 15 and 30 minutes after the injection. The area between these perpendiculars, the baseline and the systolic curve was measured in square inches with a planimeter accurate to 1 per cent. The area was recorded as positive, i.e. the systolic pressure above the base or original pressure or negative, if the line was below the baseline. The areas were divided into three groups as follows: (1) area 0.20 square inches and over, (2) area between +.19 to —.19, inclusive, and (3) area under —.20 inclusive. The first group is considered the normal response, the second group is not significant and perhaps due to random error and the third group is the under reactive or schizophrenic group.

Results and Discussion

1. *Relationship of Age to Atropine Response*

The distribution of response between two age groups, i.e. 30 years and under and 31 years and over is shown in Table 1 for the total group. There was no significant effect of age upon the atropine response.

TABLE 1

Frequency Distribution of Atropine Response by Age

	RESPONSE		
Age	Normal	Error	Schizophrenic
Young	60	37	36
Old	62	41	35
N=271	X^2=0.13	P>0.05	

2. *Relationship of Diagnosis to Atropine Response.*

There is a very clear effect of diagnosis on atropine response. Schizophrenic patients more often showed the decrease in systolic blood pressure first described by Hoffer (1954). Table 2 shows the frequency distribution of patients who had not been tested when the original data was reported. Because the relationship remained very good, it was combined with data from the earlier study for an examination of the whole group.

TABLE 2

Frequency Distribution of Atropine Response by Diagnosis for the Group Previously Not Reported and for the Total Group

	RESPONSE		
Diagnosis	Normal	Error	Schizophrenic
New Group			
Schizophrenic	31	23	38
Others	41	19	14
N=166	X^2=11.06	P<.01	
Entire Group			
Schizophrenic	49	51	61
Others	73	27	10
N=271	X^2=40.61	P<.001	

3. *Relationship of Diagnosis to Atropine as Influenced by Weight.*

The same quantity of atropine was given to all patients regardless of weight or sex. It is possible the dosage should be regulated by weight if not by sex. The distribution by weight is shown in Table 3.

TABLE 3

Frequency Distribution of Atropine Response by Diagnosis for the Entire Group as Related to Weight

	RESPONSE		
Diagnosis	Normal	Error	Schizophrenic
Effect on Weight Alone			
Ligth	40	26	8
Heavy	41	39	44
N=198	X^2=15.85	P<.001	
Effect of Diagnosis in Light Group			
Schizophrenics	21	19	6
Others	19	7	2
N=74	X^2=3.46	Not significant	
Effect of Diagnosis in Heavy Group			
Schizophrenics	19	23	39
Others	22	16	5
N=124	X^2=17.89	P<.001	

Patients were grouped into two groups (1) a light group, i.e. 130 pounds and under and (2) a heavy group, i.e. 131 pounds and over.

It is clear that weight does play a major role in the response. Each weight group was therefore examined independently for atropine—diagnosis response. This distribution for the light and the heavy group is shown in Table 3. Apparently the atropine test discriminated only amongst the heavy group of patients.

The atropine test was based on the sympathetic response to atropine on the assumption that a maximal stimulus was required. The relationship to weight indicates that too much atropine was given to the light group. Three mg. atropine in the light group produced a normal response in 45 percent of the group whereas in the heavy group only 23 percent gave a normal response.

This suggests patients over 130 lbs. should receive 3 mg. atropine and patients under 130 lbs. 2 mg.

4. *Relationship of Diagnosis to Atropine Response as Influenced by Sex.*

Since the majority of patients in the light group are female, it is possible the weight difference is due to the effect of sex. For this reason, the distribution of atropine response to sex is shown in Table 4.

TABLE 4

Frequency Distribution of Atropine Response by Sex

	RESPONSE		
Sex	Normal	Error	Schizophrenic
Male	41	39	45
Female	81	39	26
N=271	$X^2=16.77$	P<.001	

There is a significant relationship of response to sex. The frequency distribution of response to diagnosis by sex is therefore shown in Table 5.

TABLE 5

Frequency Distribution of Atropine Response to Diagnosis by Sex

	RESPONSE		
Diagnosis	Normal	Error	Schizophrenic
A. *Female*			
Schizophrenic	35	29	21
Others	46	10	5
N=146	$X^2=17.03$	P<.001	
B. *Male*			
Schizophrenic	14	22	40
Otheres	27	17	5
N=125	$X^2=27.27$	P<.001	

Apparently male and female patients respond in the same way to atropine.

This is evident in Table 6. There it is seen again that with 3 mg. of atropine there is a discrimination only in the heavy group of patients regardless of whether they are male or female. There were too few light males for analysis.

TABLE 6

Frequency Distribution of Atropine Response to Diagnosis by Sex

	RESPONSE		
Diagnosis	Normal	Error	Schizophrenic
A. *Light Females*			
Schizophrenic	20	16	5
Others	16	6	2
N=65	$X^2=1.95$	Not significant	
B. *Heavy Females*			
Schizophrenic	10	8	12
Others	10	2	0
N=42	$X^2=9.66$	P<.01	
C. *Heavy Males*			
Schizophrenic	9	15	27
Others	12	14	5
N=82	$X^2=11.46$	P<.01	

5. *Relationship of Diagnosis to Atropine Scores.*

Hoffer[3] developed an "atropine score" on the basis of the response of temperature, systolic pressure and leukocytes to atropine. This score satisfactorily discriminated between a small group of schizophrenic patients and others. The range in score between 0 and 4 was then considered normal and between 5 and 11 abnormal. All the patients were therefore scored again using the same criteria. The results are given in Table 7. It is seen that this scoring system does indicate a difference between the two groups although it could not be used as a diagnostic test. There is a tendency for more schizophrenic patients to score high values. Thus 43 out of 152 schizophrenic patients scored between 9 and 11 whereas only 8 out of 98 other patients had this score.

TABLE 7

Frequency Distribution of Patients by Atropine Score and Diagnosis

	ATROPINE SCORE	
Diagnosis	0 - 4	5 - 11
Schizophrenic	31	121
OthersOthers	45	53
N=250	$X^2=18.31$	P<.01

A large number of patients not diagnosed schizophrenic scored high on the atropine test. There are therefore several possibilities (1) that the atropine score is an artifact, (2) that psychiatric patients in general score high or (3) that a substantial proportion of our group are undiagnosed schizophrenic patients.

The first possibility is ruled out by the significant distribution difference shown in Table 7. The third possibility is probably more correct. Lewis and Piotrowski (L and P) scores for six different patient groups are shown in Table 8.

TABLE 8

L and P Scores for Six Psychiatric Groups of Patients

Group	Number	Score
Schizophrenic	159	4.20
Neurotic	54	1.40
Neurotic Depression	11	0.64
Psychotic Depression	6	1.50
Psychopathy	25	0.54
Others	12	1.00

The schizophrenic mean score was significantly greater than that of all the other groups examined. The mean value was also somewhat higher than that reported by Lewis and Piotrowski,[6] i.e. 3.5. However, it is possible the difference is not significant. However, the mean for the entire group of patients not schizophrenic is 1.10 (N=107). This is greater than the mean score reported by Lewis and Piotrowski for neurotics and depressed patients who do not subsequently become schizophrenic. If we assume that 25 per cent of this group are undiagnosed schizophrenics then the calculated score using Lewis and Piotrowski means of 0.30 for those who remain free of schizophrenia and 3.5 for those who are and will become schizophrenic is 1.10. Certainly a substantial number of patients in this series with high L and P scores were most unusual neurotics and depressions and in the opinion of one of us (A.H.) were schizophrenics. However, due to the doubtful validity of psychiatric diagnosis, it remains for time to determine how many of our high scoring patients not considered schizophrenic will clearly become schizophrenic in the future.

Conclusion

Schizophrenic patients generally react to 3 mg. of atropine by a decrease in systolic pressure. This may be due to a high level of sympathetic activity and therefore a decrease in responsivity. This test can not be used for diagnosis since it is not more precise than psychiatric or psychological diagnosis.

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Treatment of Depressions in Private Practice with Imipramine

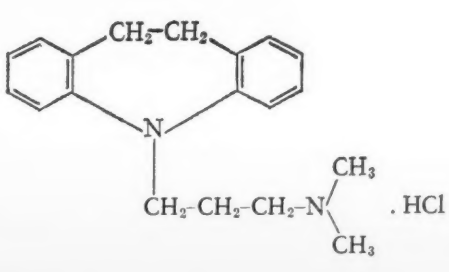
D. B. RUSKIN, M.D. and R. D. GOLDNER, M.D.

In recent years there has been an influx of new drugs in the treatment of emotional disorders. Most of these drugs have been found to successfully control the excitation, anxiety, agitation, and hyperactivity which is found to be present in many psychiatric patients. These so-called tranquilizing drugs have proven themselves ineffective in the treatment of depressive states except in patients who suffered from agitated or tension depressions. Many modes of therapy have been tried in the past in the management of depressive states. However, none of the past methods of treatment proved to be highly successful and at the same time relatively free of undesirable side effects.

Imipramine hydrochloride (Geigy — G-22355 (Tofranil®) is one of 43 iminodibenzyl derivatives which were screened for psychopharmacologic properties because of a chemical relationship to the phenothiazines. Chemically, iminodibenzyl was first described in the literature in 1899.[1] In contrast to the phenothiazines, the iminodibenzyl molecule includes two carbon atoms instead of a sulphur atom in its ring system. The compound imipramine hydrochloride is a basic alkylated derivative of iminodibenzyl (5-(3-dimethylaminopropyl) - 10, 11-dihydro-5H-dibenz (b, f) azepine hydrochloride) with the following structure:

The pharmacologic characteristics of imipramine, in laboratory tests, resembled to a large extent, those of chlorpromazine; however, the sedative, as well as the atropine-like effects, were found to be milder, and the compound was distinguished by a good tolerance and lack of toxic side reactions.[2]

$C_{19}H_{25}N_2Cl$



The original clinical investigation was undertaken over a three year period by R. Kuhn,[3] who subjected more than 500 psychiatric cases of various diagnostic categories to the drug. Contrary to chlorpromazine, this compound resulted in a psychoactivating and stimulating action in depressive states. He observed that conditions associated with over-activity, agitation, anxiety, etc., were aggravated by the compound. On the basis of this experience, it was concluded that imipramine deserved further evaluation as an antidepressant agent.

As with other agents, the mechanism of the antidepressant effect of imipramine is not understood. Action by means of a serotonin-enhancing mechanism (monamine oxidase inhibition) was excluded.[4] The clinical action of the compound, according to several investigators[5,6] is different from that of other preparations used in the treatment of depression.

While preparations such as tranquilizers, ataraxics, amphetamines, etc. as a rule counteract selected depressive symptoms only, the therapeutic effect of imipramine appears to be more comprehensive. In cases of affective psychoses, the compound in many instances included a true therapeutic effect upon depressive retardation and nihilistic thoughts, in addition to simple activation.[7]

In an attempt to clinically characterize the action of imipramine, it was concluded that the compound "deblocks" depressive manifestations rendering lysis to the mechanism producing the depression; and stimulation occurs, subsequent to the removal of the depressive factors, as a secondary effect. The action of imipramine, therefore, is characterized as thymoleptic,[5] meaning the exertion of regulatory and normalizing influence on the depressed mood level with coordination of affective sphere and ideation.

Our experiences with imipramine began in

January 1957, and this report covers a period of twenty-four months during which time the drug has been administered to over three hundred patients.

Procedure

Each author selected his own patients for study and observation. He used whatever additional therapy he considered advisable. Both authors prescribed this drug for hospitalized as well as non-hospitalized patients. The hospitalized patients were chosen from a small psychiatric unit of a general hospital, and occasionally from the medical service of the same hospital. Laboratory studies were obtained in a number of patients.

The period of observation varied from one to 24 months. The initial dosages were 25 mg to 100 mg daily. This was increased in a few patients and decreased in others. Usually the initial dosage was reduced, after one to two months, to 25 mg to 75 mg daily. Duration of medication was determined for each individual on the basis of his or her response to a gradually decreasing dosage of the drug.

A few patients received imipramine intravenously in dosages of 25 mg four times daily for a period of one to three days. This medication was then followed by oral medication with imipramine.

In all cases, the determining factor in the selection of a patient for trial therapy with imipramine was the presence of depression. This depression was expressed in a lower mood level, diminished spontaneity of thought and/or action, withdrawal from friends and/or family, complaints of psychogenic fatigue, mental oppression, slowing down of physiologic functions, constant or intermittent lack of interest, unexplainable crying, etc. No attempt was made to distinguish between clinical entities for the selection of the patient.

Other presenting symptoms were treated as indicated by past experiences of the individual author, and such treatment included the use of tranquilizers, electro-therapy, insulin sub-shock therapy, atropine-scopolamine therapy, Surital interviews, and psychotherapy. No attempt was made to isolate the symptom from the clinical complex for treatment solely with imipramine. The authors are aware that this approach is subject to criticism by various purist groups. It is also recognized that there is a definite value to double and triple blind studies for confirmatory evidence. However, this report is directed at the clinical uses and results, and it is felt that the results will establish certain useful facts upon which to base further investigation in the use of this drug in the treatment of depressions in various psychiatric conditions.

This report concerns the results in 305 patients comprising 107 men and 198 women and representing 369 diagnostic entities. Of the total, 34 were hospitalized and 261 were ambulatory or office patients. Ten, originally office patients, were admitted to the hospital for further treatment while receiving imipramine.

The age range of patients was from 15 to 77 years with the maximum number in the middle age range. Figure 1 depicts the distribution of patients according to age. A close examination by one year increments (not illustrated) reveals a marked increase in the number of patients at 26 and a marked fall-off at 47 years of age.

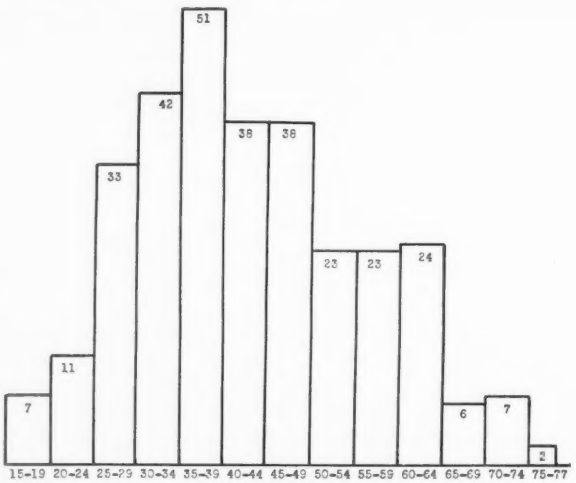


Fig. 1. Distribution of patients by age groups.

Table 1 presents the number of patients and the percentage of the total in each of the diagnostic groups represented. It is our belief that ultimate findings are not statistically significant in many of the diagnostic entities since they are each represented here by only a few patients. They are, however, being included so as to maintain a consist-

ency of thought and to point out, where applicable, beneficial results even when only one patient in a diagnostic entity is present. The bulk of the patients are found in the neurotic depression reactions, the conversion, anxiety and obsessive-compulsive neuroses, the schizophrenics, the psychotic depression reactions, the involutional depressions, the personality behavior disorders, and a moderate number of alcoholics and epileptics.

TABLE 1

Distribution of Patients, Numerically and by Percentage, According to Diagnostic Entities

Diagnostic Groups	Number of Patients	Percentage of Total
Neurotic Depression Reaction	137	37.2
Conversion Neurosis	24	6.5
Anxiety Neurosis	15	4.2
Obsessive-Compulsive Neurosis	3	0.8
Schizophrenia	17	4.6
Schizophrenia—Catatonic	2	0.5
Schizophrenia—Paranoid	6	1.6
Paranoia	1	0.3
Psychotic Depression Reaction	64	17.4
Involutional Depression Reaction	36	9.7
Personality Behavior Disorder	27	7.3
Alcoholism	12	3.3
Mental Retardation	1	0.3
Senile Deterioration	1	0.3
Cerebrovascular Arteriosclerosis	4	1.0
Organic Brain Disorder	2	0.6
Demyelinating Disorder	3	0.8
Parkinsonism	1	0.3
Menieres Disorder	3	0.8
Epilepsy	8	2.2
Post-Concussion Syndrome	1	0.3

Results

In evaluating the effectiveness of the drug, the patient's reports, the observations of relatives, nurses and physicians were all taken into consideration. Responses were catalogued as: (a) markedly improved, when the patient's condition was as good as, or better than before he was first noticed to be ill, (b) moderately improved, when the patient's condition was definitely and appreciably better than when he began treatment, but the patient needed continued help even though he was able to return to his former activities, (c) no change, when his improvement was not adequate to enable him to return to his former activities even though a definite, slight or mild improvement was noted, (d) aggravated, when the patient's symptoms became more intense or, when side effects made it necessary to discontinue the drug, and (e) no follow-up, when the patient failed to return or refused medication after only a few days trial.

The indications of improvement included mental relaxation, reduced tension, improved state of mind and mood level, increased friendliness, freedom of speech and action, improved concentration and affect, more orderly train of thought, feeling of well-being, improved appetite and increased energy.

Although both authors prescribed 75 mg daily to the larger number of their patients, one author frequently used larger dosages, whereas the other used lower dosages in many of his patients. The significance of this, in evaluating the results, can be seen in separating the patients into two groups, each representing one author. Therefore, henceforth, the two subgroups will be referred to as Group A and Group B and the combined subgroups will have no special designation.

TABLE 2

Distribution of Patients, in Groups A and B, According to Starting Dosage

Daily Dosage	Subgroups	No. of Patients A	No. of Patients B	Totals
25 mgm.	A			
	B		19	19
50 mgm.	A	2		
	B		94	96
75 mgm.	A	75		
	B		63	138
100 mgm.	A	40		
	B		9	49
150 mgm.	A	2		
	B			2
200 mgm.	A	1		
	B			1
Totals		120	185	305

Table 2 enumerates the patients started on various daily dosages. It will be observed that the patients that were started on 25 mg daily and all but two patients that were started on 50 mg daily came from Group B, whereas all of the patients that were started on 100 mg daily came from Group A.

Table 3, A and B, indicates the number in each group that improved, remained un-

changed, or were aggravated, etc., according to starting dosage. The total percentages improved, unchanged, aggravated, etc. are also presented in each group. Group A presents a total improved of 74.61% and Group B presents a total improved of 56.75%. The reason for such a difference in results can be explained by analyzing the results percentagewise for each of the different starting daily dosages. It will be seen that Group B with a total of 113 patients receiving 50 mg or less daily, suffered as a whole because of the poor results obtained from these lower dosages.

TABLES 3A AND 3B

Distribution According to Results with the Varying Dosages

TABLE 3A

GROUP A Daily Dosage	Markedly Improved	Moderately Improved	No Change	Aggravated	No Follow-up	Total
25 mgm.						
50 mgm.	1		1			2
75 mgm.	27	30	9	2	7	75
100 mgm.	18	11	7		4	40
150 mgm.	1	1				2
200 mgm.			1			1
No. Total	47	42	18	2	11	120
%	39.61	35.0	15.0	1.66	9.16	100%

TABLE 3B

GROUP B Daily Dosage	Markedly Improved	Moderately Improved	No Change	Aggravated	No Follow-up	Total
25 mgm.	4	3	5	3	4	19
50 mgm.	27	25	39	3		94
75 mgm.	22	18	21	2		63
100 mgm.	5	1	3			9
150 mgm.						
200 mgm.						
No. Total	58	47	68	8	4	185
%	31.35	25.4	36.75	4.3	2.16	99.96

In the combined groups (Table 4), 63.62% were improved, 34.42% markedly improved, and 29.2% moderately improved. Of the patients who started on 25 mg daily, 36.75% showed improvement; of those receiving 50 mg daily, 54.1% showed improvement; of those receiving 75 mg daily, 70.2% showed improvement; of those receiving 100 mg daily, 71.4% showed improvement; of the three patients receiving larger dosages daily, two showed improvement and one showed no change. Of the ten patients whose conditions were aggravated by imipramine, three received only 25 mg daily, three 50 mg daily and four 75 mg daily. None were in the groups receiving more than 75 mg daily. Of the patients who failed to follow treatment, four received 25 mg daily, seven 75 mg daily and four 100 mg daily. None received more than 100 mg daily.

TABLE 4

Results, Expressed in Percentages, Within Each Starting Daily Dosage

COMBINED GROUP Daily Dosage	Markedly Improved	Moderately Improved	No Change	Aggravated	No Follw-up	Total
25 mgm.	21.0	15.75	26.3	15.75	21.0	99.8
50 mgm.	28.1	26.0	41.6	3.1		98.8
75 mgm.	35.5	34.7	21.7	2.9	5.0	99.8
100 mgm.	47.0	24.4	20.4		8.0	99.8
150 mgm.	50.0	50.0				100.0
200 mgm.			100.0			100.0

Table 5 presents the distribution of patients according to duration of treatment and results obtained in each period-group. Although an appreciable number reported marked improvement within a few days, most of the patients noticed either (a) slowly increased improvement to maximum, in about 10 to 14 days, or (b) sudden improvement after receiving the drug for two to three weeks. In any event it was found that the optimum duration of treatment was

TABLE 5

Results According to Treatment Duration

	Duration of Medication							
	1 mo.	1-3 mos.	4-6 mos.	7-9 mos.	10-12 mos.	13-18 mos.	19-24 mos.	Totals
Markedly Improved	11	22	25	13	11	18	7	107
Moderat. Improved	11	38	16	9	5	5	2	86
No Change	49	22	13	1		1		86
Aggravated	12		1					13
No Follow-up	13							13
Totals	96	82	55	23	16	24	9	305

TABLE 6

Results Within Each Diagnostic Entity

Diagnostic Groups	Markedly Improved	Moderately Improved	No Change	Aggravated	No Follow-up	Total
Neurotic Depression Reaction	41	38	52	5	1	137
Conversion Neurosis	6	11	3		4	24
Anxiety Neurosis	5	3	3		5	16
Obsessive-Compulsive Neurosis	2	1				3
Schizophrenia	8	3	5	1		17
Schizophrenia—Catatonic	2					2
Schizophrenia—Paranoid	5		1			6
Paranoia					1	1
Psychotic Depression Reaction	27	13	13	2	9	64
Involutional Depression Reaction	12	12	11	1		36
Personality Behavior Disorder	7	7	6		7	27
Alcoholism	3	2	5		2	12
Mental Retardation		1				1
Senile Deterioration	1					1
Cerebrovascular Arteriosclerosis	1	1	2			4
Organic Brain Disorders		1	1			2
Demyelinating Disorders		2	1			3
Parkinsonism	1					1
Menieres Disorder	2		1			3
Epilepsy	4	2	2			8
Post-Concussion Syndrome				1		1
Total	127	97	106	10	29	369 in 305 pts.

TABLE 7

Results, Expressed in Percentages Within Each Diagnostic Entity, of Groups A and B

Diagnostic Groups	Markedly Improved		Moderately Improved		No Change		Aggravated		No Follow-up	
GROUPS	A	B	A	B	A	B	A	B	A	B
Neurotic Depression Reaction	41.4	26.8	27.6	27.7	27.6	40.7		4.6	3.4	
Conversion Neurosis	37.5		37.5	62.5	12.5	12.5			12.5	25.0
Anxiety Neurosis	41.6		25.0		16.6	25.0			16.6	75.0
Obsessive Compulsive Neurosis	66.6		33.3							
Schizophrenia	61.5		23.0		15.4	75.0		25.0		
Schizophrenia—Catatonic	100.0									
Schizophrenia—Paranoid		83.3				16.6				
Paranoia									100.0	
Psychotic Depression Reaction	51.9	39.0	14.8	25.0	25.9	16.6	3.7	2.7	3.7	16.6
Involutional Depression Reaction	100.0	29.4		35.3		32.3		2.9		
Personality Behavior Disorder	35.0		25.0	28.5	25.0	14.3			15.0	57.1
Alcoholism	20.0	28.5		28.5	60.0	28.5			20.0	14.3
Mental Retardation			100.0							
Senile Retardation	100.0									
Cerebrovascular Arteriosclerosis	50.0		50.0			100.0				
Organic Brain Disorder		50.0			100.0	50.0				
Demyelinating Disorders			100.0							
Parkinsonism	100.0									
Menieres Disorder	66.6				33.3					
Epilepsy	80.0			66.6	20.0	33.3				
Post-Concussion Syndrome								100.0		
Percentages of Group A and B	45.9	26.9	23.3	28.2	21.2	33.6	0.7	4.0	8.9	7.2

from three to six months. A very appreciable number of patients, however, required continuation of medication, many at a reduced dosage, for over a year in order to avoid a relapse, and some patients have had to continue with 25 mg daily for two years.

Table 6 presents the results obtained in the various diagnostic groups. The slight discrepancy in totals, from previous tables, is due to the fact that there are 369 diagnostic entities in the 305 patients represented. It will be seen from this table that no diagnostic group is completely unresponsive to this drug, with the possible exception of the single patient with post-concussion depression. In all other diagnostic groups there is a higher percentage that improved than those that did not respond or whose condition was aggravated by the drug.

Table 7 presents the same information in terms of percentages within each diagnostic group. However, the percentages refer to that portion of the diagnostic group within either subgroup A or B. It will be noted, that with a few exceptions, the percentage improved in Group A is larger than in Group B. We feel, again, that this reflects the smaller dosages used in many of the diagnostic groups in Group B.

To this point no mention has been made of the results following intravenous administration. The drug was administered intravenously in approximately 20 patients. There were no local irritations or tissue reactions and no unpleasant general side-effects from the intravenous administration. Also, there was no therapeutic advantage when the drug was administered by this route if both routes of administration were equally available. However, when the patient was catatonic, withdrawn or for some similar reason oral administration was either inadvisable or impossible, intravenous administration of 25 mg q.i.d. for three or four days brought about sufficient cooperation and improvement to make oral medication practical. We did not notice any faster response, dosage for dosage, by the use of the intravenous route.

The problem of evaluating the response to the drug for side-effects is difficult. This is true in the use of any drug, even in non-psychiatric problems and is especially true in psychiatry where the patient's emotional response to a drug is often a major factor. Thus a patient may present symptoms because he reacts adversely to a drug on an emotional plane. In others, a patient's symptoms, formerly masked by the intensity of the presenting complaints, may become more important to the patient once the presenting complaints are relieved. And lastly, some of the resultant reactions may be an inherent property of the drug, based on its actions elsewhere in the body. These latter reactions may be beneficial or annoying to the patient. It is a question whether these reactions should be termed side-effects. However, the true interpretation of the term side-effects is a subject in itself, and we merely refer to the above problem in order to establish the fact that the authors do not consider all the symptoms reported below to be true side-effects. The fact that patients report these reactions, however, justifies their inclusion in this report. Many of these reactions were relieved by reduction of dosage, others by addition of some other drug, and still others subsided merely by continuing the therapeutic program.

TABLE 8

Common Reactions in Number and Percentage of Total Patients

Symptom	No. Patients	%
Dry Mouth	73	23.7
Perspiration	53	17.4
Increased Tension	48	15.7
Weight Gain	38	12.5
Constipation	25	8.2
Sex Suppression	18	5.9
Hot Flashes and Cold Chills	14	4.6
Bitter Nauseating Table	13	4.2
Headache	9	3.0
Sex Stimulation	7	2,3
Blushing and Flushing	6	2.0
Dizziness	3	1.0
Anorexia	3	1.0

The more common complaints with their frequency of occurrence in the 305 patients are indicated in Table 8. It will be noted that increased tension occurs in 48 patients. This complaint is amenable to correction by the addition of a mild tranquilizer, and therefore, it does not present as much of a therapeutic problem as some of the less frequent

complaints. The complaints of dry mouth and perspiration are very annoying to the patient. Both symptoms may be relieved by a reduction in dosage. The complaint of dry mouth may also be relieved by sucking a hard candy or chewing gum. Occasionally a cathartic is required to relieve constipation. The question of weight gain can be a problem in female patients, especially if they were not underweight at the beginning of the treatment. The gain is partly due to an improved appetite. However, some weight gain seems to come from an altered physiology following administration of the drug. Sex suppression appears to be a definite physiological effect of the drug when it occurs. The patient affected reports that he is less interested in sexual matters and less able to consummate the sex act satisfactorily. On the other hand, the complaint of sexual stimulation appears to be an indirect result of a general improvement of mood and feeling of physical fitness.

Hot flashes, cold chills, and blushing and flushing seem to be vasomotor disturbances due to an emotional reaction to the drug rather than the direct effect of the drug itself. Observation of the patients with these complaints has allowed us to witness the subsidence of these complaints by adding a mild tranquilizer in most cases. The headaches, dizziness and anorexia can be avoided by relieving the patient's anxiety.

In addition to the above complaints, one or two patients reported several other symptoms as listed in Table 9.

TABLE 9

Infrequent Symptoms in Combined Group

Symptoms reported by 2 patients	Symptoms reported by 1 patient
Drowsiness	Gastric disturbance
Blurred vision	Numbness
Confusion	Abnormal feeling of head
Tinnitus	Burning sensation
Weight loss	Nocturia
Irregular menses	Feeling of stiffness
Weakness	Abnormal relaxation

Those reactions which can properly be considered a property of the drug, are: dry mouth, perspiration, weight gain, constipation, sex suppression and bitter nauseating taste. Table 10 presents the frequency of these reactions according to the starting daily dosage. Considering the total number of patients represented in each dosage group, it is obvious that, except for the very high dosages, an increase in dosage does not increase the number of reactions to the drug.

TABLE 10

Six Common Reactions in Patients at Various Starting Daily Dosage

Daily Dosage / *Reactions*	25 mgm.	50 mgm.	75 mgm.	100 mgm.	150 mgm.	200 mgm.	Total
Dry Mouth	5	37	25	5		1	73
Perspiration	4	25	18	6			53
Weight Gain		22	13	3			38
Constipation	1	6	9	7	1	1	25
Sex Supression	2	8	5	3			18
Bitter Nauseating Taste	1	5	6	1			13
Totals	13	103	76	25	1	2	220
Total in Group	19	96	138	49	2	1	305

One finding, not reported above, is a drop in blood pressure in a large number of patients. This was found primarily in those patients who had been suffering from an increased blood pressure due to emotional difficulties. The drop was the natural accompaniment to the relief of these difficulties. This drop in blood pressure caused no difficulties or unpleasant reactions except in one patient who was simultaneously receiving Diuril. This patient reported a brief period of dizziness which occurred early in the morning on getting out of bed. This was relieved on withdrawing the Diuril. Blood pressure readings had to be taken before arising and 30 minutes after arising, and the blood pressure was found to be back to normal for the individual. The patient at no time experienced faintness or disturbance of consciousness.

The eight patients suffering from epilepsy with abnormal electroencephalographic records showed no evidence of aggravation of their convulsive disorders. Improvement of the patient's mood, in a few cases, made it easier to obtain cooperation in treatment of the epilepsy. The one exception was a patient who was also an alcoholic and refused to cooperate unless he were allowed to continue drinking.

The laboratory procedures failed to reveal any deviations from normal.

Discussion

Imipramine used to relieve the depression frequently present in mentally ill patients, has proven to be effective in a high percentage of patients treated. Its effectiveness has been witnessed in numerous diagnostic entities and is not limited to the endogenous depressions or the functional disorders. Imipramine is an antidepressant and not a stimulant. This function of the drug is evident when the anxiety is secondary to the depression, in which case the anxiety is relieved rather than aggravated. Relief of the anxiety parallels relief from the depression. Although its most remarkable results are in the alleviation of the depression symptom, *per se,* its effects are not limited entirely to that part of the symptom spectrum. Patients frequently reported that delusional thoughts and hallucinations became more vague—"like a bad dream that occurred a long time ago," and they became less introspective and less ruminative. With an improvement of mood, there is a reduced intensity of obsessions and compulsions and a lessened intensity of paranoid ideas. With an improvement of mood there is also an improvement in the patient's response to physical disabilities. This was strikingly demonstrated in a patient who had reached a plateau of response to anti-Parkinson drugs and was very depressed at the state of his neurological illness. He had been advised that the drug would have no effect on the neurological illness. The addition of imipramine caused the patient to report a marked improvement in his Parkinson symptoms after three days of medication. It was later proved, first through repeated neurological examinations, and second, by repeatedly withdrawing and reinstituting the drug, that his improvement was due to mood change. Each time the patient received imipramine he felt as if he had improved. The same effects could not be obtained when using other antidepressants or stimulants such as Marsilid or Ritalin.

Imipramine has also exposed a masked anxiety, or when the anxiety was apparent, it frequently aggravated this symptom. This was noticed when the anxiety appeared to precede the depression. This effect of the drug was also noticed in the presence of hostility. In the case of anxiety, it was usually possible to overcome this problem by prescribing a suitable tranquilizer. However, it was more difficult to control hostility while the imipramine was continued. A striking example of this problem was observed when a patient was admitted to the Neuropsychiatric Department in a catatonic state. The day after admission the patient failed to respond to any of the personnel, neglected all duties regarding personal appearance or personal hygiene, spent the day on the floor and was vegetating. At this point, imipramine was administered intravenously. In all, three intravenous injections of 25 mg each were administered that day. Shortly after the third injection, the patient arose, attended to her personal appearance and to the appearance of her room, requested nourishment, and joined in with the other patients' activities. She had a normal sleep that night. The next day she began to take imipramine orally at a dosage of 25 mg q.i.d. She continued to mingle with the other patients, but as the day wore on she became belligerent and before nightfall insisted that she be released from the hospital.

Not all catatonic schizophrenics react in this manner as exemplified by another patient who, on receiving 25 mg, q.i.d. intravenously for three days, gradually became more accessible and on the fourth day was responding normally. Following seven additional days of oral administration of 100 mg daily, she had recovered sufficiently to be discharged to outpatient care.

Many patients who responded adequately within six months were able to discontinue the medication and have not had to resume medication to date. However, an appreciable number of patients have had to continue the drug, some for as long as 24 months. Most of these patients could be maintained in optimum condition with 25 mg daily. However, some patients required the full original daily dosage in order to maintain the improvement. Since depressions are noted for their exacerbations and remissions, it is quite possible that those patients who

were able to discontinue the drug may have to resume medication in the future.

Many patients received other forms of treatment while receiving imipramine. It was quite apparent that this drug enhanced the effect of electrotherapy and sub-shock insulin. Results were more favorable, and treatments were frequently reduced in number. The patient could then be maintained as an outpatient with imipramine with further continued improvement. Many patients who would have been considered suitable for either electrotherapy or insulin therapy did not require these more drastic therapies because of the use of imipramine. Several patients who had previously received electrotherapy without beneficial results responded dramatically to imipramine. Also, by removing the despair or diminishing the intensity of the depression, imipramine made the patient more accessible for psychotherapy. By using imipramine we were able to avoid or forestall any evidence of the precipitation of depressions by tranquilizers. There was no buildup of tolerance to imipramine during a period of 24 months. Medication discontinued for various reasons was just as effective, dosage for dosage, when again instituted as during the first administration. Patient reactions to the drug occurred within the first month of administration and could be tolerated by the patient. Occasionally a small reduction of dosage reduced the intensity of the reaction. At other times, addition of a tranquilizer, cathartic, etc., made possible continuation of the drug at the original dosage. At no time was the reaction alarming or serious to the patient's general health.

Summary

There were 305 patients in 369 diagnostic entities, given imipramine in dosages varying from 25 mg to 200 mg daily. Patients were selected on the basis of the presence of depression or symptoms indicative of a basic depression. Other therapies were used as indicated.

Improvement varied from 36.75% in those patients who received an initial daily dosage of 25 mg to 71.4% in those patients receiving an initial daily dosage of 100 mg. Only those patients who were able to return to their former state of relative well-being were considered improved. The majority of patients were able to discontinue medication in six months, others needed continuation of medication over a period of two years. These latter patients were usually able to continue their state of improvement on a reduced dosage.

Side-effects were generally mild and did not contradict the continuation of the medication. The more severe reactions usually responded to reduction of dosage or by the administration of a tranquilizer.

Conclusion

On the basis of the results obtained, imipramine has excellent properties as an antidepressant without serious side-effects.

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120 North Michigan Ave., Saginaw, Michigan.

Electrocardiographic Non-Specific T Wave Changes in Psychiatric Patients

GEORGE H. SWEENEY, M.D., JOHN N. FORREST, M.D., and ALPHONSE TELFEIAN, M.D.

Over the last few years opinion has grown in the medical and psychiatric departments at the Albany Hospital that reports of "non-specific T wave changes" were more common in the electrocardiograms of psychiatric patients than in other hospitalized patients. Review of the literature has revealed a lack of agreement on the incidence of non-specific T wave in these two groups. This disparity together with our own confusion on the subject has prompted us to analyze the electrocardiograms of a large group of psychiatric and surgical patients seen here in the last year.

Review of Literature

In 1945 Loftus and his associates[1] studied 41 patients suffering from personality disorders with intense emotional reactions and found only one T wave and one P wave abnormality not associated with heart disease. They were unable to determine the conditions under which emotion might evoke electrocardiographic change. Mainzer and Krause,[2] in 1940, demonstrated T wave changes in 16 of 53 surgical patients, and attributed the change to fear of operation. No control group was used. Ruskin[3] and associates studied the electrocardiograms of 100 severe mental cases in 1947, free of cardiac disease, and found 26 non-specific T wave changes. They suggested definitely that neurosis and functional psychosis cause abnormal T waves. No control group was used in this study. Wendkos and co-workers,[4] in 1944, reported T wave changes in 80% of patients referred for cardiovascular survey because of functional symptoms related to the cardiovascular system. The number of patients was not mentioned and no control group was used. Precordial lead abnormalities were taken as positive in spite of inconsistency in these leads noted by Wendkos. Logue[5] and his associates, in 1944, reported 67 T wave changes in 150 patients diagnosed as neurocirculatory asthenia. No control group was used. White and his group,[6] in 1947, reported 8 of 35 patients with neurocirculatory asthenia to show non-specific T wave changes, but stated these to be in type and frequency comparable to those found in a study of 1000 normal subjects. It may be noted that incidence of 25-35% is common in these references representing several very different groups surveyed.

Clinical Material

For the purpose of this study non-spe ific T wave changes consist of flattening, diphasic, or inverted T waves in one or more leads. File cards were obtained at random from electrocardiogram records of 100 surgical and 100 psychiatric patients treated in the last year at this general hospital. All surgical services were included. Most psychiatric patients were on a closed ward but over 10% were on the general open floors. Most patients had only one electrocardiogram, and the file report chosen was accepted for the purposes of this study. The cardiac status was evaluated by a cardiologist (J.F.) for evidence of gross heart disease with the following criteria: (1) Electrocardiographic evidence of infarction, or other electrocardiographic evidence of definite myocardial disease, (2) X-ray evidence of organic heart disease (cardiomegaly, congestive failure, or great vessel abnormality), or (3) obvious clinical evidence of organic heart disease (congestive failure, ischemic heart disease, or evidence of valvular disease). The hospital record from which the electrocardiogram was taken was used to obtain the information evaluated here. Records were found for 99 psychiatric and 98 surgical patients; the others were not available. Two of the three missing records referred to patients without T wave abnormality.

From the Department of Psychiatry and Medicine, Albany Hospital, Albany, N. Y.

It was assumed that the psychiatric patients represented greater emotional abnormality than the surgical patients. As tranquilizing drugs were in general use only on the psychiatric service, their use was recorded to see whether any specific T wave effect was present, and to evaluate the possible lessening of emotional intensity which might in turn influence T wave abnormality incidence if this depended on severity of affect disturbance.

Results

Direct comparison of the two groups showed 31 psychiatric patients to have T wave changes. Ten of these 31 had significant heart disease based on the criteria given above. Of 98 surgical patients, 31 had non-specific T wave changes and 12 of these 31 had significant heart disease.

Of the 31 psychiatric patients with T wave changes 25 were over 50 years of age, and of the 31 surgical patients with T wave changes 29 were over 50 years of age. All the surgical and psychiatric patients without T wave changes fell into normal age frequency distributions. Patients with heart disease were eliminated from the groups with T wave changes. The T wave changes are unexplained in 19 surgical and 21 psychiatric patients. The incidence is seen to be the same.

An analysis of the incidence of T wave changes in patients on tranquilizers was made. Four of the surgery patients were on these drugs—one on Equanil, two Thorazine, and one reserpine. None of these had T wave changes. Of the 99 psychiatry patients, 79 were on tranquilizers prior to electrocardiograms—45 on Sparine, 21 Thorazine, 8 Equanil, 3 reserpine, 1 Frenquel, and 1 Pacatal. Of those on tranquilizers 25 had T wave changes. Eliminating patients with heart disease, 18 or 23% of those on tranquilizers showed unexplained T wave changes. All of the patients on tranquilizers with non-specific T wave changes had received either Sparine or Thorazine, but these were the only drugs given to significant numbers of patients in this group. Of psychiatric patients receiving either Sparine or Thorazine 68% received Sparine, and 67% of patients on tranquilizers with unexplained T waves had received Sparine. No direct influence of tranquilizers on T wave incidence has been demonstrated.

TABLE I

	Surg.	Psych.	Tranquilizers(P)
Total	98	99	79
With T wave change	31	31	25 (32%)
With heart disease	12	10	8
Unexplained T changes	19	21	17 (23%)

Of the psychiatric patients, 17 had electroconvulsive treatment prior to electrocardiogram. Seven had T wave changes, and when those with heart disease were subtracted four had unexplained T wave changes. None of the surgery patients had electroconvulsive treatment prior to their electrocardiograms. Though the size of the group of 17 precludes any really significant conclusion on this point, no direct influence of electroconvulsive therapy on T wave formation is apparent.

Discussion

All results tabulated show remarkable uniformity of the relative frequencies of T wave changes in the surgical and psychiatric patients studied. Heart disease and T wave changes were more common in the older age groups, but there was essentially no difference in the incidence of either phenomenon between the psychiatric and surgical patient groups, and there was the same incidence of unexplained T waves in each group when cardiac disease was eliminated. Assuming that more severe emotional stresses were operative in the psychiatric than the surgical patients, the hypothesis of emotional influence upon T waves would seem to be disproved. Diagnoses of all patients were widely varied and it would seem unlikely that the surgical patients as a group were more disturbed than the psychiatric. If small groups of patients within either category had had emotional factors (e.g. anxiety) which might be alone responsible for T wave changes, one would expect a few more of these in a group severely enough disturbed to be hospitalized; in most cases this required a locked ward. Usually electrocardiograms were taken within a day or so of admission. Our incidence of non-specific T wave changes is essentially the same as that reported (25%) by Dr. White's group in 1000 normal subjects.

Tranquilizers were given essentially only to the psychiatric patients, and cases are included which were treated with most of the common tranquilizers. To determine whether tranquilizers had a direct effect on T wave incidence, we found that 32% of psychiatric patients on tranquilizers had T wave changes and 31% of all psychiatric patients had T wave changes. Eliminating patients with heart disease, 23% of those on tranquilizers showed unexplained T wave abnormality-incidence approaching that found in all groups studied. The incidence of T wave changes unexplained by heart disease was the same when corrected for the relative numbers receiving Sparine and Thorazine. The number of patients receiving the other tranquilizers was not statistically worth evaluating, but in fact none of these few had T wave changes. It would appear from our group that Sparine and Thorazine have no direct effect on T waves.

We cannot be certain that the use of tranquilizers in the psychiatric patients prior to electrocardiograms did not reduce anxiety or some other factor influencing T wave, and thus indirectly bring T wave incidence down to that of the surgical patient group. The exact agreement of incidence figures between the two large groups suggests that no significantly causative differences exist, but positive proof is not possible from this series.

Yet another limitation of this series is that drugs were usually started only a few hours or a day prior to taking of the electrocardiogram, so that the true effect of the drug cannot be considered to have been fairly established in many cases. Since we see no positive reason for assuming effect of tranquilizers on T wave, we did not attempt to artificially limit the groups studied here with respect to duration of tranquilizer dosage.

Conclusion

The remarkable similarity of incidence of T waves in the psychiatric and the apparently control group of surgery cases leads the investigators to conclude that no significant effect of emotional factors upon the formation of electrocardiographic non-specific T waves has been demonstrated. We believe that previous uncertainty in the literature has come from study of groups too small to be significant, and lack of comparison with control groups.

Summary

Comparison of incidence of electrocardiographic non-specific T wave changes in 99 psychiatric and 98 surgical patients in a general hospital shows 31 of the psychiatry patients to have such change. Ten of these had significant heart disease; 31 of the surgical patients had T wave changes, and 12 of these had significant heart disease. Most of the patients in both groups with T wave changes were older than the mean of the group, and even more of the patients with heart disease in both groups were older than median. Eliminating cases of definite organic heart disease, 19 of the surgery and 21 of the psychiatry patients had unexplained non-specific T wave change. No difference was noted in T wave incidence between psychiatric patients receiving tranquilizers and surgical patients without them, and neither Sparine nor Thorazine influenced these incidences.

We see no evidence for believing psychiatric conditions influence electrocardiographic non-specific T wave incidence significantly.

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Clinical Experience with Fluphenazine

G. DONALD NISWANDER, M.D., and ISMET KARACAN, M.D.

Fluphenazine was first used in January 1958 at the Arthur P. Noyes Institute for Neuropsychiatric Research. The initial problem at that time was to determine dosage of the substance as a potential tranquilizing agent. On the basis of experimental animal data, it was calculated that the compound was approximately 25 times more potent than another phenothiazine derivative, trifluprom azine. Accordingly, four chronic male schizophrenic patients were administered three mg. of the compound for one week. The dosage was then increased weekly by two mg. throughout a four week period. At the same time, four similar patients received a placebo medication.

Between the third and fifth week of medication (dosage 6 to 10 mg.) an obvious and continuing tranquilizing effect was first observed in three of the patients, in that they were less anxious, socialized better, and fewer psychopathological symptoms were elicited during a mental status examination. The fourth patient was dropped from the study during the fourth week, when he developed a marked hypotensive side-effect, while receiving eight mg. of the compound.

Purposefully, in an attempt to induce extra-pyramidal symptoms, a toxic side-effect frequently observed with phenothiazine derivatives, the medication was further increased to 14 mg. daily in the three patients. At this dosage level one of the three developed the characteristic extra-pyramidal symptoms of muscle spasm, cog-wheel rigidity, masked facial expression, etc. These symptoms cleared within 48 hours when the medication was discontinued. No changes were observed in the patients receiving the placebo medication. In view of this initial screening study it was recommended that between 6 to 10 mg. of the substance be prescribed for a tranquilizing effect.

Later in the year, the study at the Noyes Institute was expanded and the compound has been prescribed for an additional 91 patients. The following reports the results and observations of the study.

Selection of Patients

Patients selected for the study can be divided into two groups; first, a group of 73 patients recently admitted to the receiving area in the hospital, and second, a group of 18 chronic hospitalized patients.

In the first group, all had been ill only a short period before hospitalization. The group consisted of 40 males and 33 females; the ages ranged from 15 to 75 years, with a median age of 37 years. When the medication was prescribed the patients had been hospitalized 14 days to 210 days, with a median time of 120 days. The patients were selected to receive the medication only for the reason that some tranquilizing agent would have been prescribed.

TABLE I
Diagnostic Categories

Diagnosis	No. Pts.	
	Recent Admissions	Chronic
SCHIZOPHRENIC REACTIONS		
Catatonic Type	19	6
Paranoid Type	9	1
Acute Undifferentiated Type	3	
Chronic Undifferentiated Type	3	5
Schizo-Affective Type	2	
Hebephrenic Type		2
MANIC-DEPRESSIVE REACTIONS		
Manic Types	9	2
Depressed Types	2	
PSYCHONEUROTIC REACTIONS		
Anxiety Type	6	
Depressive Type	4	
Conversion Type	1	
INVOLUTIONAL PSYCHOTIC REACTIONS	5	
MENTAL DEFICIENCY		
With Psychosis	4	2
Without Psychosis	1	
CHRONIC BRAIN SYNDROMES, MIXED GROUP	3	
PERSONALITY DISORDERS	2	
TOTALS	73	18

From Arthur P. Noyes Institute for Neuropsychiatric Research, New Hampshire State Hospital, Concord, New Hampshire.

Fluphenazine (Prolixin, trade mark) was supplied by The Squibb Institute for Medical Research, New Brunswick, New Jersey.

The chronic group of patients was composed of six male and 12 female patients. The ages ranged from 21 to 77 years, with a median age of 37 years. The duration of hospitalization ranged from 1.5 years to 31.5 years, with a median duration of 4 years. All of these chronic patients had at one time or another been tried on various tranquilizing medication without improvement.

The diagnostic categories of both groups of the patients are shown in Table I.

Observations

The clinical picture was evaluated periodically in terms of the mental status examination, i.e., appearance and behavior, stream of talk, mood, affect, content of thought, and sensorium. In addition, socialization and ward behavior were appraised from the psychiatric nursing notes.

Dosage and Duration of Medication

The dosage of fluphenazine in all patients varied according to the individual patient's needs. The dosage range of the medication has been from as low as 0.5 mg. daily to as high as 15 mg. daily.

The period for receiving the medication varied also as the study progressed. At the writing of this report, the time intervals are as follows:

Time	Patients
1-4 weeks	35
5-8 weeks	12
9-12 weeks	31
13 weeks +	13

Results

Both groups of patients were rated either improved or unimproved after receiving the medication. As stated, this rating was based on the mental status examination and the ward notes.

Table II shows the response to the medication according to diagnosis in both groups of patients.

Side Effects

In both groups of patients extra-pyramidal symptoms, parkinsonian-like in nature, occurred in twenty-eight individuals; 11 were males and 17 females. The symptoms appeared while the patients were receiving various dosage levels of fluphenazine outlined as follows:

Mg. per day	Patients
15	10
10	7
7.5	4
6	3
4	2
5	1
3	1

The extra-pyramidal syndrome (side-effect) disappeared within 48 hours after the dosage was reduced.

Restlessness, "jittery feelings," and insomnia were complaints in a few patients.

TABLE II

Response to Medication

RECENT ADMISSIONS

Diagnosis	No. of Pts. Treated	Improved	Unimproved
SCHIZOPHRENIC REACTIONS			
Catatonic	19	12	7
Paranoid	9	5	4
Acute Undifferentiated	3	2	1
Chronic Undifferentiated	3	0	3
Schizo-Affective	2	1	1
MANIC DEPRESSIVE REACTIONS			
Manic	9	8	1
Depressed	2	1	1
PSYCHONEUROTIC REACTIONS			
Anxiety	6	4	2
Depressive	4	3	1
Conversion	1	1	0
INVOLUTIONAL PSYCHOTIC REACTIONS	5	4	1
MENTAL DEFICIENCY			
With Psychosis	4	3	1
Without Psychosis	1	1	0
CHRONIC BRAIN SYNDROMES	3	0	3
PERSONALITY DISORDERS	2	0	2
TOTAL	73	45	28
		63%	37%
CHRONIC GROUP			
SCHIZOPHRENIC REACTIONS			
Catatonic	6	4	2
Chronic Undifferentiated	5	1	4
Hebephrenic	2	1	1
Paranoid	1	1	0
MANIC DEPRESSIVE, MANIC	2	1	1
MENTAL DEFICIENCY WITH PSYCHOSIS	2	0	2
TOTAL	18	8	10
		44%	56%

These symptoms subsided when the dosage was lowered.

In all patients, the systolic blood pressure dropped 10-30 mm. of mercury. Two patients (3 mg. daily) in addition to the patient in the initial screening, developed a moderate hypotensive reaction, which gradually returned to normal levels within a week after the medication was discontinued.

No other side effects, such as skin reactions, were observed. No changes were found in the blood picture and liver function studies.

Discussion

Fluphenazine is an effective tranquilizing medication in both recently admitted psychiatric patients and in the chronic mentally ill individual. Results percentage wise in this study, in both groups of patients, in terms of improvement, agree with results with other tranquilizing medications, such as the many phenothiazines, the rauwolfia group, etc.

The high incidence of extra-pyramidal symptoms in this study actually occurred as a result of deliberately starting the patients on large doses of the medication. As stated, these symptoms subsided in all patients when the amount of drug was reduced. On the other hand, in view of the fact that parkinson-like symptoms occurred over a wide dosage range in this study, the physiologic individualization of the patient should be kept in mind when using this phenothiazine or any other related substance.

In most instances the recently admitted group of patients responded to smaller amounts of the medication than the chronic patients. More striking in the recently admitted patient group was the observation that in spite of initial dosage a maintenance dose of 1 mg fluphenazine sustained the improvement, once the patient responded to the medication. This suggests, as the early experimental animal studies seemed to indicate, that fluphenazine is a long-acting phenothiazine.

In the recently admitted group 13 have been discharged from the hospital and medication was discontinued. No recurrence of symptoms have been reported. Eight other patients have been discharged on a maintenance dose of 1 mg. fluphenazine daily and are being followed in the out-patient department. Of the balance 21 are still in the hospital on a maintenance dosage of one mg., receiving further rehabilitation in anticipation of release from the hospital; the other four patients are receiving larger doses of the compound (4-8 mg.). In both groups those who failed to respond to the medication have had other treatment prescriptions, e.g., other tranquilizers, convulsive therapy, etc.

The chronic patients responded as expected, with a lower incidence of improvement and in general, with a requirement for more medications.

From this study, the authors would recommend the following manner of use of fluphenazine. In the recently admitted patient, improvement is noted usually within the first week of treatment in those patients who respond to the medication. A starting dosage of 3 to 6 mg. daily will usually benefit the patient, if he is going to respond to the medication at all. Once improvement is noted, the dosage can usually be reduced to one mg. daily. In some cases the drug must be titrated to meet the patient's individual dosage requirement.

In the chronic group, 4 to 8 mg. fluphenazine daily seem sufficient to begin treatment and maintain an improved condition once it has occurred. The chronic patient responds slower, and should be given the medication for at least a three or four week period.

Comparison of Autopsy and Clinical Diagnosis on Psychiatric Patients

BENJAMIN ROTHFELD, M.D.

Introduction

There is a paucity of studies in the literature on correlation of clinical and autopsy findings. In the available literature I found only three such studies.[1,2,3] None dealt with psychiatric patients. In two of these the study was in terms of the frequency with which various diseases were missed. The third paper dealt not only with the number of times a given diagnosis was not found but also why the diagnosis was missed. It would appear that the third approach is a more valuable one in terms of profiting from past mistakes and improving diagnostic acumen.

Since no previous work correlating autopsy with clinical diagnosis had been done in psychiatric patients, it was thought that such a study would be of interest. With this in mind, 100 consecutive autopsies done on psychiatric patients at the Perry Point Veterans Hospital between January 1954 and November 1957 were reviewed. Where there was a discrepancy between the autopsy and the clinical diagnoses an attempt was made to find the reason. The reasons were grouped according to a modified classification of Gruver and Freis.[1]

Results

The following table shows the results obtained. Number of diagnoses missed because of:

TABLE 1

a. Lack of patient cooperation	13
b. Failure to order routine test	2
c. Missed physical finding	2
d. Failure to account for abnormal sign or symptom	2
e. Failure to order appropriate test	4
f. Failure to account for abnormal lab or x-ray finding	1
g. Misleading normal x-ray	4
h. Acceptance of previous diagnosis	2

Out of the 100 autopsies there was a total of 18 mis-diagnoses or 18%. This compares with 11.6% in Munck's series and 6% in Gruver and Freis.

The following table lists the number of times the various diagnoses were missed:

TABLE 2

Pulmonary embolism	2
Lobar pneumonia	4
Hydronephrosis	1
Coronary occlusion	1
Subdural hematoma	1
Retroperitoneal abscess	1
Subacute bacterial endocarditis	1
Gastric ulcer	1
Miliary TBC	1
Acute pancreatitis	1
Bronchogenic carcinoma	1
Liver carcinoma with widespread metastases	1
Peptic ulcer of esophagus with rupture into pericardium and tamponade	1
Acute peritonitis following prostatectomy	1

The following cases illustrate the various causes for mis-diagnoses:

a. Lack of patient cooperation.

Case 14: J.H. was 65 at the time of death. He had been hospitalized at Perry Point since 1926. He had been delusional and hallucinating for years before his death. His course was uneventful medically till June 1954 when he was discovered unconscious on the floor of the shower room and died a few minutes later. He was signed out as a cerebral accident but autopsy revealed myocardial infarction with rupture and cardiac tamponade.

Comment: It is difficult to see how this case could have been diagnosed ante mortem in the absence of complaints by the patient or the occurrence of dramatic signs of a vascular accident. Not uncommonly the only clue to a myocardial infarction is a statement by the ward personnel that a patient "just doesn't look quite right."

Case 18: S.D. was a 59 year old male Negro admitted to Perry Point VAH, on 6-21-55 by ambulance. He had been sent from Washington, D.C., with the information that he had been confused since 6-10-55 and had a left hemiplegia since 6-14-55. Lumbar puncture was said to be crystal clear in Washington. On examination patient was confused but tried to cooperate in the examination. On physical examination he showed a left hemiplegia with hyperactive deep tendon reflexes on the left. He was diagnosed as having cerebral thrombosis with

From the Medical Service, VAH, Perry Point, Md.

left hemiplegia. His course was progressively downhill and he expired on 7-1-55.

Autopsy revealed bilateral subdural hematoma as the cause of death.

Comment: In the absence of a history of trauma, the above diagnosis was not suspected. However, since the patient's course was not typical of a stroke, a higher index of suspicion would have led to a spinal tap and EEG which might well have given clues to the correct diagnosis.

Case 83: W.S. was 61 at the time of his death. He had been hospitalized at Perry Point since 1948 with a diagnosis of chronic brain syndrome. He was hostile to ward personnel with multiple complaints all through his hospitalization. In late 1956 it was observed that he was losing weight and generally appeared to be going downhill. He refused all diagnostic studies. On March 25, 1957 he developed chills and fever, course was progressively downhill and he expired 3-28-57.

The clinical diagnosis was arteriosclerotic heart disease.

Autopsy revealed: 1. Hydropericardium due to gastric fluid. 2. Peptic ulcer of the esophagus, ruptured into the pericardium.

Comment: In this case, it is highly probable that if the patient had been more cooperative, a barium study of the esophagus and G.I. series would have been done months before, the diagnosis would have been made and definitive therapy instituted. However, despite his refractoriness, it is felt that these studies might well have been obtained with more vigorous efforts. Most likely with the aid of ataractics and barbiturates, a tube could have been passed and barium deposited in the esophagus and stomach.

b. Failure to order routine test.

Case 1: Z.J. was 79 at the time of his death. He was admitted to Perry Point in November 1953 with a diagnosis of chronic brain syndrome associated with cerebral arteriosclerosis. In December 1953 he developed urinary retention and was transferred to the infirmary service where a catheter had to be inserted. He had several febrile episodes during the two months he was hospitalized. These were attributed to urinary infections and the patient had no chest x-ray done other than that on admission. His course was progressively downhil and he expired 1-20-54.

Autopsy revealed multiple emboli. There was no evidence of urinary tract infection.

Comment: Although pulmonary emboli often do not produce any alteration in the chest x-ray, the one chance to have made the diagnosis in this case was by x-ray. Ordinarily when patients are admitted to the infirmary ward and develop a temperature elevation, a chest x-ray is done. In this case, most likely because the urinary tract seemed so likely a source of fever, no chest x-ray was done.

c & f. Missed physical finding and failure to account for an abnormal lab or x-ray finding.

Case 21: J.R.P. was 67 at the time of death. He had been a patient at Perry Point since 1928. His medical course was uneventful till May 1956 when an anal mass was noted and a biopsy was read as transitional cell carcinoma. Shortly thereafter a Miles abdominal perineal reaction was done. Subsequently his course was steadily downhill. A week before death, one observer felt that he had a mass in his right lower abdomen. However, other observers did not agree. Also for a week before death, blood count ranged between 15,000 and 28,000 with a marked shift to the left. In spite of this, no reexploration was done.

Autopsy revealed a retroperitoneal abscess in the right lower quadrant with necrosis of the right ureter.

Comment: In this case both the persistent leukocytosis and the debated mass in the right lower quadrant were clues to the correct diagnosis and they were both overlooked.

d. Failure to account for abnormal sign or symptom.

Case 25: J.E.S. was 67 at the time of his death. He had been hospitalized at Perry Point since 1943 following a cerebral accident with resultant right hemiplegia and aphasia and psychotic reaction manifested by emotional instability. His medical course was uneventful till February 1956 when he ran a low grade temperature for a few days. He had a similar episode in March 1956. No cause was found for these temperature elevations. On 6-14-56 he developed a temperature elevation of 103. There were physical findings suggestive of left lower lobe pneumonia but chest x-ray was negative. He continued to run a fever despite penicillin, units 600,000 daily. His course was progressively downhill and he expired 6-22-56.

Autopsy revealed: 1. Subacute bacterial endocarditis with vegetations on the aortic crisps. 2. Encephalomalacia left temporal lobe (old).

Comment: Although this patient had three episodes of unexplained fever over a four month period, no blood cultures were obtained. Thus the one treatment which offered a possibility of survival, massive doses of penicillin, was not used.

e. Failure to order appropriate test.

Case 42: J.L. was 72 years old at the time of his death. He had been hospitalized at Perry Point since 1922. In 1951 he was found to have diabetes. In mid January 1956 he developed a left epididymitis with subsequent abscess formation. This subsequently drained through the scrotum and resulted in the formation of a persistent sinus tract. Culture revealed hemolytic Staph albus. Course was progressively downhill and patient expired 2-4-56.

Autopsy revealed: 1. Miliary tuberculosis. 2. Tuberculosis epididymitis.

Comment: Although culture was done for pyogenic organisms, no smear or culture was done for tuberculosis. Although the diagnosis of miliary tuberculosis is often quite difficult, in the above case it would appear that a diagnosis of tuberculosis could have been established fairly easily and the appropriate treatment instituted.

g. Due to misleading normal x-ray.

Case 35: R.B.W. was 72 years old at the time of his death. He was admitted to Perry Point in 1952. He had been hospitalized on a psychiatric ward elsewhere since 1949. In 1950 he was operated on for a perforated peptic ulcer. The ulcer was sutured at this time. In January 1956 he developed auricular fibrillation and cardiac failure. This responded fairly well to digitalis. In early March 1956 he developed melena. Two G.I. series were negative. Barium enema and proctoscopy were negative. Melena persisted off and on and on 3-31-56 he suddenly went into shock and died.

Autopsy diagnosis was massive exsanguination into gastrointestinal tract due to ulcer of stomach.

Comment: In a patient in better physical condition an exploratory operation might have been tried because of the persistent melena. However, in this patient with his precarious cardiac staus it is understandable why this was not done in the face of two negative G.I. series.

h. Due to accepting previous diagnoses.

Case 91: J.C. was 65 at the time of his death. In January 1957 he was found to have benign prostatic hypertrophy. A cystotomy was done on 2-7-57. On 2-13-57 he developed signs and symptoms of an acute coronary occlusion and went into failure. He responded well to bedrest, salt restriction and digitalis. The second stage of the prostatectomy was deferred till June 1957 because of his coronary occlusion. On June 18, 1957 a suprapubic prostatectomy was done. On June 19, 1957 there was a sudden drop in blood pressure and shock developed. Despite oxygen and levophed, patient's course continued downhill and he expired on June 20, 1957. Patient's temperature rose to 102° the day before death and ran a spiking course until death.

Autopsy revealed: 1. Acute localized peritonitis, following prostatectomy. 2. Pulmonary edema.

Comment: Since the second stage operation was undertaken with some trepidation because of the previous cardiac history, it was understandable that his postoperative shock should be ascribed to a new coronary occlusion. However the spiking temperature during the 24 hours before death was not characteristic of a coronary occlusion and should have alerted the clinicians to the possibility of sepsis.

Discussion

As can be seen from Table 1 the most common reason for mis-diagnosis is lack of patient cooperation, which in most cases consisted of inability of the patient to give an adequate history or to cooperate in indicated examinations. In current medical teaching the importance of the history is stressed and laboratory findings are played down. This is responsible in good part for many of the above diagnostic failures. That history is of less importance in psychiatric patients is recognized, but frequently there is no concomitant recognition that laboratory work assumes great importance in these patients. Thus signs which ordinarily would not be a reason for ordering laboratory work in non psychiatric individuals, might be important diagnostic clues in a psychiatric patient. For example, the fact that an individual didn't look quite himself on a given day would not be an indication for an ECG in a non-psychotic individual but might well be the only sign of a coronary occlusion in a psychiatric patient. In addition, more stress should be placed on slight deviations from normal in laboratory findings. Thus an elevation in white count might be the only clue to an occult infection.

Many disorders in psychiatric patients present themselves in a manner entirely different from that seen in non-psychiatric patients. If this is accepted and the increased value of laboratory work in this population is recognized, there would be a marked improvement in diagnostic accuracy.

As far as the patient's failure to cooperate in indicated examinations it has been noted in many cases that with moderate sedation with barbiturates or by means of premedication with ataractics, most examinations can be carried out on otherwise uncooperative patients.

Summary

1. One hundred consecutive autopsies in psychiatric patients have been surveyed and the clinical diagnoses compared with those obtained at post mortem.

2. The cases in which there was a discrepancy between the two diagnoses have been analyzed and attempt made to classify the reasons for the difference.

3. Suggestions for improving the accuracy of diagnosis in this group of patients have been made.

A Clinical Study of the Anticonvulsant Properties of Meratran

ROBERT E. OTT, M.D. and ROBERT H. MCMASTER, M.D.

The central stimulant drug, Meratran,* has been found to possess a protective activity against the maximal electroshock seizure in mice in a dose which approximately parallels that which produces stimulant activity. This anticonvulsant effect in animals supplements that of phenobarbital and phenacetylurea and is independent of the stimulating effect of Meratran.[1]

Most available anticonvulsant agents useful in the therapy of grand mal epilepsy commonly cause sedation as a side effect. In an effort to overcome this effect and to enhance patient acceptance of the anticonvulsant drugs, various central stimulants have been tried. Fabing[2] has reported encouraging results with Meratran in the control of drowsiness induced by anticonvulsant therapy in epileptic patients. Targowla[3] administered Meratran in a daily dose of 3.0 mg. to 4.0 mg. concurrently with anticonvulsants to six epileptic patients with good response. In each case, the drug was administered only to counteract the soporific effects of the anticonvulsants and no effort was made to determine its effect on seizure frequency. In view of the unique finding of anticonvulsant properties in a drug which is otherwise a central stimulant, a controlled clinical study was undertaken to determine the effects of Meratran on seizure frequency in epileptic patients.

Material

This study was conducted at the Gallipolis State Institute, Gallipolis, Ohio, which is now functioning as an institution for the care and treatment of the mentally deficient although it was known formerly as the Ohio Hospital for Epileptics. Of the 2,241 patients currently in residence at the Gallipolis State Institute, 1,483 are epileptics.

It was necessary to accept for the study patients who were already on some type of anticonvulsant therapy, since all epileptics in the hospital were under treatment. In order that the number of variables could be kept to a minimum, only patients who had been incompletely controlled on phenobarbital alone were selected. A group of 40 such epileptic patients was equally divided into experimental and control groups, comparable in age, sex, I.Q., and clinical status. During the experimental period, all patients under observation continued to receive the individualized doses of phenobarbital which they had been receiving for thirteen to nineteen months prior to the study. These doses varied from 60 to 500 mg. daily. The 10 male and 10 female patients in the experimental group were placed on adjunctive Meratran therapy.

Method of Study

The dose of Meratran for the experimental group was established initially at 2.5 mg. three times a day, purely on an empirical basis. After two months of such therapy, the dose of Meratran was increased to 5.0 mg. three times a day, because of encouraging results in the reduction of seizure frequency and the absence of adverse side reactions. Therapy with Meratran was continued at the higher dose level for 12 months, during which period the observations analyzed below were made.

In order that no special attention would be attracted to individual patients under observation, no change was made in the method of reporting and recording of seizures from that which has been in use at the Gallipolis State Institute for some years. Each cottage or ward submits a daily report listing the number of seizures observed in each patient during the previous 24 hour period. Grand mal seizures are recorded as major attacks; all other types of seizures (e.g. psychomotor, petit mal, minor motor, and myoclonic) are listed as minor attacks or "symptoms." Seizure data are entered daily on each patient's

*Meratran is the trademark of The Wm. S. Merrell Company, Cincinnati 15, Ohio, for its brand of pipradrol (alpha-(2-piperidyl) benzhydrol hydrochloride).

calendar card. In addition, ward physicians keep an up-to-date record of each patient's anticonvulsant medication and any changes made therein. Duplicates of those records are required on each ward. The attendants responsible for administration of medication were not informed of the possible pharmacologic effects of Meratran. However, as the study progressed, some of them became aware of increase in activity and alertness and decrease in frequency of seizures in some of the patients which they could only ascribe to the "new" medicine.

Results and Analyses

For purposes of simplified presentation, data for male and female patients have been combined. When responses in the sexes differed significantly they are mentioned. Data for both the control and experimental groups are presented, although there is some question of their comparability. While roughly similar in age, I.Q. and duration of condition (Table I), the experimental group is characterized by an initial higher frequency of major seizures (Table II). It will be noted (Table II) that the mean frequency of seizures for the control group increased 21.4 per cent during the treatment period while that of the experimental group decreased 30.1 per cent.

Table III shows the comparison of the mean numbers of major seizures per month for each patient for each of the two periods. The pairs of means, together with the variations, are also shown in Table III. For example, patient C.B. in the control group averaged 5.95 major seizures per month during the pre-Meratran period and 5.08 major seizures each month during the period of Meratran therapy, with the difference of —0.87, indicating lesser frequency of seizures during the Meratran period. Inspection of Table III reveals a tendency in both control and experimental groups toward more frequent reduction in seizures among female patients. This difference is greater in the experimental group in which the seizures were reduced in 9 of 10 women but only in 6 of 10 men.

Table IV shows the number of patients in each group having relatively fewer, the same number, or more major seizures during the course of therapy with Meratran. Of the 20 patients in the experimental group 15 had fewer major seizures during the period of Meratran therapy. The other five patients in this group had more seizures during the treatment period. On the other hand, 14 of the control group had more and six had fewer major seizures during the same period. The disproportionately large number of patients in the experimental group showing fewer seizures under Meratran treatment is significantly different from chance expectation: $p = .03$. When the size of the difference between means is taken into consideration, the results are even more significant: $p = .01$ (Wilcoxon matched-pairs signed-ranks test).[5]

Analysis of the data was also made in terms of the number of seizure-free months for both groups for the two periods. The mean number of seizure-free months for each patient for each period, together with the difference, are shown in Table V. These data are summarized in Table VI. There is a decrease in the percentage (35.0 per cent to 25.8 per cent) of seizure-free months in

TABLE I

Patient Characteristics

	Control Group	Experimental Group
Age		
Range	13–60	10–71
Median	46.5	39.5
Mean	39.9	40.0
I.Q.		
Range	8–108	5–111
Median	45.5	44.0
Duration of Condition (Years)		
Range	10–56	9.5–49
Median	30	27.5
Mean	28.6	32.6

TABLE II

Seizures Per Month

	Control Group		Experimental Group	
	Mean	Per Cent Change	Mean	Per Cent Change
Major Seizures				
Pre-Meratran period	1.76		4.09	
Meratran period	2.24	+21.4	2.86	—30.1

TABLE III

Comparison of Major Seizures per Month for Pre-Meratran Period (M_1) and Meratran Period (M_2)

CONTROL GROUP				EXPERIMENTAL GROUP			
Patient	M_1	M_2	M_2-M_1	*Patient*	M_1	M_2	M_2-M_1
Female				Female			
CB	5.95	5.08	—0.87	CW	3.14	1.42	—1.72
LC	1.77	3.92	+2.15	ES	0.42	0.92	+0.50
RG	0.79	0.67	—0.12	DG	1.84	0.42	—1.42
CM	3.21	1.75	—1.46	HB	10.53	5.17	—5.36
HM	1.05	0.67	—0.38	FJ	5.89	3.42	—2.47
MM	0.42	0.92	+0.50	MK	3.00	2.42	—0.58
RP	0.05	0.50	+0.45	MS	4.05	0.92	—3.13
LS	0.00	0.25	+0.25	LW	3.11	0.75	—2.36
AS	0.58	0.42	—0.16	HG	9.53	8.50	—1.03
SS	0.00	0.33	+0.33	EJ	6.47	3.67	—2.80
Male				Male			
WH	3.47	5.67	+2.20	EG	9.25	3.75	—5.50
RJ	4.58	5.50	+0.92	JK	1.84	1.17	—0.67
LK	1.32	2.67	+1.35	EC	1.16	0.17	—0.99
WK	0.95	2.25	+1.30	WK	1.68	2.58	+0.90
GK	2.53	2.25	—0.28	EM	2.63	4.67	+2.04
RR	0.74	1.33	+0.59	HN	2.89	1.92	—0.97
AT	3.11	4.25	+1.14	MP	1.74	3.00	+1.26
CW	1.32	1.92	+0.60	GP	2.79	3.00	—0.79
GW	1.11	1.92	+0.81	RG	4.16	6.25	+2.09
WW	2.26	2.50	+0.24	RE	6.21	4.17	—2.04

TABLE IV

Variations in Seizure Frequency During Meratran Therapy

	Number of Patients with Major Seizures		
	Fewer	Same	More
Control Group	6	0	14
Experimental Group	15	0	5

the control group but an increase (10.2 per cent to 23.8 per cent) in the experimental group. Table VII shows the variation in seizure-free months during the period of Meratran therapy. Whereas 15 of the control group had fewer seizure-free months during this period, 13 of the experimental group had more seizure-free months. The imbalanced distribution for the experimental group is highly significant: $p = .02$.

The possibility that reduction in seizures with Meratran therapy was related to age, I.Q., or duration of condition was tested by means of the rank difference correlation method. A moderate but significant relationship ($rho = .43$; $p = .05$) was found between age and difference between mean number of major seizures per month for the two periods, indicating that in general the older the individual the more beneficial the effect of Meratran. No relationship was found between the other two variables and the frequency of seizures.

After the original study had been in progress for four months, indications that Meratran had anticonvulsant activity led us to add it to the anticonvulsant medication of a group of nine patients who had been poorly controlled on phenobarbital and one or more of the following drugs: diphenylhydantoin sodium, methyl - phenyl - ethyl - hydantoin, mephobarbital, and trimethadione. This group received, in general, 2.5 mg. Meratran three times daily for a period of two months, followed by 5.0 mg. three times daily for ten months. However, during the course of Meratran therapy, changes were made in the usual anticonvulsant regimen in those patients who showed little or no response so that statistical analysis of this small group is not possible.

Some interesting observations in this group of patients merit comment. Five of the nine patients showed a reduction of 60

TABLE V

Comparison of Seizure-Free Months for Pre-Meratran Period (M_1) and Meratran Period (M_2)

CONTROL GROUP				EXPERIMENTAL GROUP			
Patient	M_1	M_2	M_2-M_1	*Patient*	M_1	M_2	M_2-M_1
Female				Female			
CB	.21	.00	—.21	CW	.00	.50	+.50
LC	.38	.08	—.30	ES	.74	.75	+.01
RG	.63	.58	—.05	DG	.05	.58	+.53
CM	.21	.17	—.04	HB	.00	.00	.00
HM	.58	.50	—.08	FJ	.11	.00	—.11
MM	.74	.50	—.24	MK	.21	.25	+.04
RP	.95	.67	—.28	MS	.00	.42	+.42
LS	1.00	.92	—.08	LW	.11	.58	+.47
AS	.47	.58	+.11	HG	.00	.00	.00
SS	1.00	.67	—.33	EJ	.00	.00	.00
Male				Male			
WH	.05	.00	—.05	EG	.00	.08	+.08
RJ	.00	.00	.00	JK	.16	.58	+.42
LK	.47	.25	—.22	EC	.26	.83	+.57
WK	.26	.08	—.18	WK	.42	.25	—.17
GK	.05	.17	+.12	EM	.05	.08	+.03
RR	.37	.42	+.05	HN	.05	.08	+.03
AT	.05	.00	—.05	MP	.16	.00	—.16
CW	.42	.25	—.17	GP	.16	.17	+.01
GW	.42	.17	—.15	RG	.00	.08	+.08
WW	.16	.17	+.01	RE	.00	.00	.00

TABLE VI

Seizure-Free Months

	Control Group	Experimental Group
Pre-Meratran period	35.0%	10.2%
Meratran period	25.8%	23.8%

TABLE VII

Variation in Seizure-Free Months During Meratran Therapy

	Number of Patients with Seizure-free Months		
	Fewer	Same	More
Control group	15	1	4
Experimental group	3	4	13

per cent or more in the average monthly number of grand mal seizures. Three of the patients showed a remarkable reduction in such seizures, although they were not completely controlled; for 23 months immediately prior to receiving Meratran, these three patients had an average monthly grand mal seizure rate of 15.4, 13.5, and 36.8. The respective monthly averages for the 12 month period during which Meratran was administered were 0.3, 1.5, and 1.8. All three patients received phenobarbital and diphenylhydantoin sodium prior to and during the period of therapy with Meratran.

Certain side effects following the administration of Meratran appeared in this group, none of which had been observed in the original group of patients. The patient who had a reduction in monthly seizure rate from 15.4 to 0.3 was eventually taken off Meratran therapy because of delusions and hallucinations. This patient had exhibited these reactions prior to receiving Meratran and their exacerbation was not unexpected since such a phenomenon had been reported previously.[4] Another patient had increased evidence of a pre-existing anxiety state but not to the point where discontinuation of Meratran therapy was required. Several patients in this group were more alert mentally while taking Meratran than they were preceding its administration.

Conclusions

1. The anticonvulsant activity of Meratran in human beings partially controlled on phenobarbital is demonstrated. The results

were statistically significant based on the following criteria:

a. reduction of the average monthly grand mal seizure rate;

b. the increase in number of seizure-free months.

These results reflect general improvement but not complete control of seizures in any one patient.

2. This statistical significance is evident when the seizure record of the experimental group is compared with

a. the record of the same group of patients for an adequate period prior to the experiment, and

b. the seizure record of a control group of patients for similar periods of time before and during the experiment.

3. Undesirable side effects (central stimulation) occurred uncommonly.

4. Desirable manifestations of central stimulation, such as increased mental alertness, decreased drowsiness, and increased motor activity, were noted in some of the patients.

5. Synergistic or additive effects between Meratran and other combinations of anticonvulsant agents were indicated by clinical observation in a small group of patients, although results were not subjected to statistical analysis.

Summary

A group of 40 epileptic patients who had previously received only phenobarbital as an anticonvulsant were divided into two comparable groups in regard to age, I.Q. and sex. One group was given Meratran therapy; both groups continued phenobarbital therapy at the same dosage level they had been receiving prior to this study.

Statistical analyses indicate that clinically Meratran exhibits a significant anticonvulsant effect and simultaneously overcomes some of the soporific effects of phenobarbital.

Further indications of the anticonvulsant activity of Meratran were found clinically in a small group of patients who had received combinations of phenobarbital and one or more of the other anticonvulsants prior to and during Meratran therapy. The greatest reduction in seizures during treatment with Meratran occurred in this group.

Central stimulating effects of Meratran therapy, when present, were for the most part favorable: increased alertness, less drowsiness, increased motor activity. Undesirable side effects occurred in two patients whose pre-Meratran psychiatric condition indicated a tendency to anxiety or hallucinations.

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Basic Statistical Concepts in Medical Research

CONRAD M. AYRES, M.D.

Statistics is the science of facts. The essence of the statistical method is that, when we use it properly, we are comparing like with like. In this connection, the following quotation from *The Lancet* seems appropriate:

> However great may be our aversion to figures . . . the solution of most of the problems of clinical or preventative medicine ultimately depends on them. Any assessment of success or failure . . . based on fact rather than on opinion must nearly always be expressed in numerical form.[1]

The statistical method has assisted medical science in evaluating etiological factors and forms of prevention and treatment of diseases. Zubin points out the role of statistical observations in the discovery of the etiology of general paresis.[2] Up to about 1900, the etiological factors of general paresis were considered to be, in the main, night air, emotional tension, and mercury. These beliefs arose from observations showing that many paretics had a history of night life and night work, and were actors or artists leading highly emotional lives. The mercury occasionally used for treatment of syphilitic manifestations was then erroneously considered to be the cause of the cerebral damage responsible for general paresis.[3] Statistical findings of the significant association of syphilis with general paresis prompted the search for the spirochetae in the brain of the paretic, and thus led to the discovery of the luetic etiology of general paresis. Present-day evidence of the possible etiological role of cigarette smoking in lung cancer is also largely based on statistical data.[4] A 5-year statistical follow-up study on lobotomy cases by Zubin and others has disproved the validity of lobotomy as a treatment of schizophrenia.[5,6] Kallman's classic work offers statistical proof of the existence of a gene-controlled recessive element in schizophrenia and of the prevalence of consanguinity among parents of psychotics.[7,8,9]

Presented at a meeting of the Eastern Psychiatric Association, Dec. 19, 1958.

I. Valid Comparison

In experimental medical research, the system of alternate allocation, by which cases are placed alternately in two groups (for example, a treated and an untreated group), may be reasonably relied upon to equalize these groups in all characteristics except the one under examination—in this example, treatment. This system forms the basis for the valid comparison of groups, providing the research worker with random samples, that is, with test and control groups representative of patients with the particular condition under study. On rare occasions, it is possible to use the same patients as their own controls in a different experiment.

Experimental groups of patients not obtained by the alternate system of allocation are biased or selected samples, reflecting the natural subjectivity and selectiveness of the experimenter. However, the system of alternate allocation does not obviate the necessity of testing whether the groups thus obtained are, in fact, equal in all the characteristics believed to be relevant. Once the prerequisites for the valid comparison have been fulfilled, one may proceed to the recording and study of experimental observations.

II. Collection of Data

The systematic listing of all the data under study is called the medical research work sheet.[10] The elements which the research scientist usually records in his work sheet during the course of his observations are shown in Figure 1.

From the unsorted mass of data of the work sheet, it is impossible to detect the relationships among the various observations. For this purpose the data must be organized into *statistical tables* and their visual representations, namely *graphs or diagrams*. To recognize the most relevant elements in a particular research project is left to the individual researcher who, though not necessarily an expert in statistics, is expected to be fully conversant with his specialized field.

BRONX AFTERCARE CLINIC—DECEMBER 1958
BASIC STATISTICAL CONCEPTS IN MEDICAL RESEARCH

MAIN ELEMENTS OF THE MEDICAL RESEARCH WORK SHEET

AGE, SEX, CIVIL STATUS, AND GENETIC TYPE
PERSONALITY AND EMOTIONAL PROBLEMS
BACKGROUND:
- RELIGION, CULTURE AND RACE
- FAMILY HISTORY
- PERSONAL HISTORY

DEFINITION OF ILLNESS:
- TYPE, DURATION, SEVERITY, COMPLICATIONS, ETC.

ETIOLOGY OF ILLNESS:
- ETIOLOGICAL, CONTRIBUTING, AND PRECIPITATING FACTORS

TREATMENT (PREVIOUS, THERAPEUTIC AND MAINTENANCE):
- FORMS, DOSAGES AND DURATION
- SIDE EFFECTS:
  - Allergic Reactions (Histamine Release):
    - Asthma, Headache, Nasal Congestion, Pruritus, Skin-Rash, etc.
  - Hemodynamic Reactions:
    - Hyper and Hypotension, Dizziness, Shock, etc.
  - Neurologic Syndromes:
    - Dystonia, Parkinson-like Reactions, Sympathetic Imbalance, etc.
  - Thermic Reactions:
    - Fever and Hypothermia
  - Toxic Reactions:
    - Hepatic, Hematic, Nephropathic, Neuropathic, etc.

LENGTH AND FREQUENCY OF OBSERVATIONS:
- BEFORE, DURING, AND AFTER TREATMENT

Figure 1. Elements of the Medical Research Work Sheet.

III. Presentation of Data

1. *Statistical Tables.* Statistical tables should be self-explanatory necessitating no reference to the text. The first step in tabulation is to divide the test group and the control group into subgroups, each containing the individuals considered to be similar or alike in a given characteristic, for example, age in decades, or type of schizophrenic reaction. This is called the subgrouping or classification of observations, or frequency distribution. In constructing a frequency distribution, 5 to almost 15 subgroups or classes are usually appropriate.

When dealing with groups based on elements measured by numerical factors (e.g., age, or duration of illness), it is best to keep the group intervals at constant size. When the groups are based on elements not measurable by numerical factors, such as schizophrenic reaction types, all the types involved must be included in the subgrouping. Further subdivision of groups, or focusing the attention on a special group or groups, may then be in order.

*Distribution by Age and Diagnostic Type in a Random Group of 186 Female Convalescent Schizophrenics.**

DISTRIBUTION	NO.	PERCENT	REHOSPITALIZATION NO.	REHOSPITALIZATION PERCENT
AGE GROUP:				
10-19†	7	4%†	1	14%†
20-29	43	23%	11	26%
30-39	66	36%	16	24%
40-49	40	21%	5	13%
50-59	24	13%	0	0%
60-69†	6	3%†	0	0%†
TOTAL	186	100%	33	18%
DIAGNOSTIC TYPE:				
CATATONIC	41	22%	10	24%
PARANOID	72	39%	10	14%
MIXED	54	29%	11	20%
SIMPLE†	4	2%†	1	25%†
HEBEPHRENIC†	12	6%†	1	8%†
CHILDHOOD†	3	2%†	0	0%†
TOTAL	186	100%	33	18%

*OMITTED: Observations on Male Patients, Rehosp. Time and Mos. Hosp. Care.
† Data not considered in text because of small number of cases.
Highest percentage in total group.
Highest rate of rehospitalization.

Figure 2. Sample of Statistical Table.

2. *Graphs.* Graphs or diagrams are devices which facilitate visual grasp; they should be presented as an addition to tables, not as a substitute for them. The three main types of graphs used in medical writing[10] are: bar, circular, and linear diagrams.

a. *Bar diagrams* are used to show discontinuous types of observations, or observations on different groups of subjects, by means of bars or solid columns of different length on a background rectangular grid.

Distribution of 33 Female Schizophrenics Who Required Rehospitalization

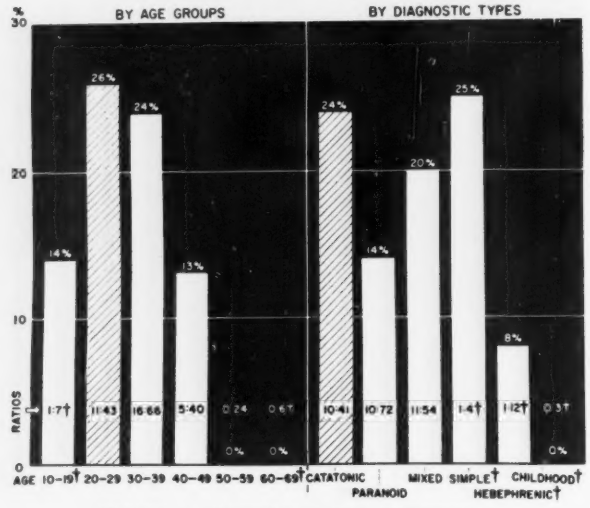

Figure 3. Sample of Bar Diagram.

Rehospitalizations in a Random Group of 186 Convalescent Female Schizophrenics Divided Into Two Subgroups:

1. Patients Treated with Electro Convulsive Treatment (ECT).
2. Patients *Not* Treated with ECT.

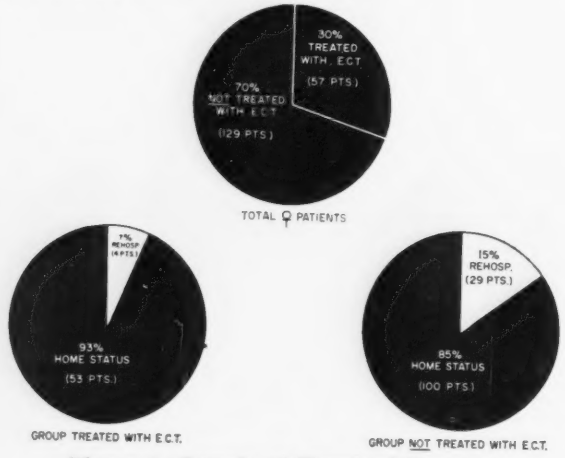
30% TREATED WITH E.C.T. (57 PTS.)
70% NOT TREATED WITH E.C.T. (129 PTS.)
TOTAL ♀ PATIENTS
7% REHOSP. (4 PTS.)
93% HOME STATUS (53 PTS.)
GROUP TREATED WITH E.C.T.
15% REHOSP. (29 PTS.)
85% HOME STATUS (100 PTS.)
GROUP NOT TREATED WITH E.C.T.

Figure 4. Sample of Circular Diagrams.

b. *Circular diagrams* are used to show the proportion of the various parts of a group to the whole, when the parts are few, and there is no change in the time element.

c. *Linear diagrams* are used to show continuous observation on the same subjects, by means of a line, called the diagrammatic line, plotted over a rectangular grid with both vertical and horizontal background lines.

IV. Scales, Rates and Ratio

1. *Scales.* Scales are used for the recognition of measurements in rectangular types of

SERPASIL STUDY—1955
Observations on 50 Adolescents

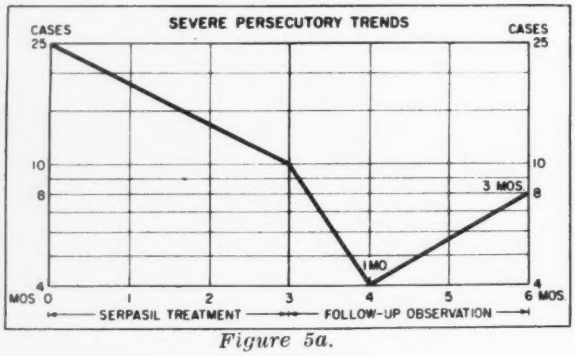

Figure 5a.

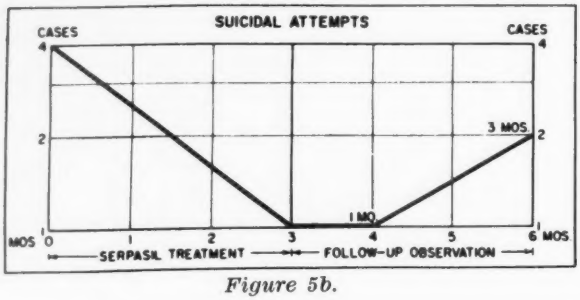

Figure 5b.

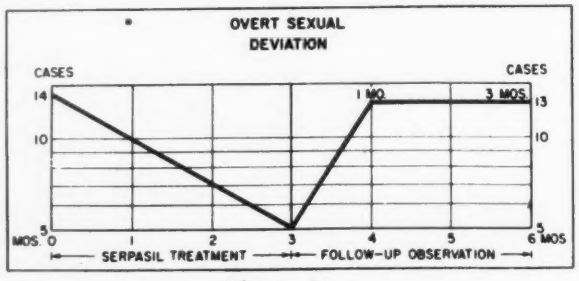

Figure 5c.

Figure 5. Sample of Linear Diagrams.

diagrams, that is, in bar and linear diagrams. The comparative values of bars and diagrammatic lines are measured by reference to two perpendicular lines, a horizontal one called the axis of the abscissae, and a vertical one called the axis of the ordinates. A background grid consisting of a system of coordinate lines parallel to the two axes helps in the visual recognition of values.

In bar diagrams, the vertical coordinates are often not required; in linear diagrams, both vertical and horizontal coordinates are always required. The values indicating the units of measurement of the scales are shown at the top of the axis of the ordinate, and at both ends or below the axis of the abscissae. Reference values are located in correspondence to the grid lines at the left and

at the bottom of the graph; occasionally also at the right and top.

The scale of the bar diagram must always have an arithmetic progression which is uniformly spaced, while the scale of the linear diagram may have either an arithmetic or a logarithmic progression, the latter being logarithmically spaced.[13] The arithmetic scale may refer to any type of observation, continuous or discontinuous, in the same subjects or in different subjects; the logarithmic scale refers only to continuous types of observations in the same subjects Logarithmic or log scales are made up of logarithmic cycles and they are especially useful for comparisons of *changes* in rates. Equal changes of rates in the actual data are represented by equal rises and falls in the logarithmic graph.

Values of time, the independent variable with constant progression, must always be represented by an arithmetic scale. This progression is conventionally shown below the axis of the abscissae in correspondence to the ordinate lines. When the time element is to be considered in a diagram containing logarithmic cycles for the abscissal coordinates, a mixed type of grid must be used—with uniform spacing for the ordinate lines and logarithmic spacing for the abscissal coordinates. This type of diagram with mixed grid is called semi-logarithmic or semi-log diagram. Commercial log graph paper shows directly the value of the original numerical figures in correspondence to the log grid ruling. Accordingly it may not be necessary for the experimenter to look up the logarithms of the original values since these may be plotted directly on commercial graph paper.

2. *Rates.* A rate is a proportion or ratio to a numerical value kept constant. Thus, we may have rates of per 1, per 10, per 100, per 1,000, per one million, etc. The rate most frequently used is the rate per 100 or per cent. A standardized rate is called an index or unit.

In *statistical tables,* a column with rates is often used to facilitate comparison. However, even when rates are included in statistical tables, the original data should be given at full value. The mere publication of rates or of other values descriptive of the frequency distribution, as for example, the arithmetic mean or average (to be discussed below) is definitely inadequate and lessens the value of the data to others.

V. Averages and Range

1. *Averages.*

An average is a measure of the general numerical position of a group of observations. There are three types of average in common statistical use: the arithmetic mean or average, the median, and the mode or modality.

A. *Mean or arithmetic average,* also termed the average, is the sum of all the observations, divided by their number.

B. *Median* is the central value of a series when all the values are listed in order, from the lowest to the highest, or vice versa. The median may be calculated directly when the total number of observations is an odd number; with an even number of observations, the median is calculated as the mean of the two central values.

C. *Mode or modality* is the most frequent value recurring in a series of observations. When there is no predominance of identical measurements, the mode is approximately calculated as follows: Mode = Mean—3.

2. *Range* is a measure commonly used in medical reports and is expressed by the two values at the extreme limits of the observations, namely the highest and the lowest.

3. *Ratio:* Ratio is a reciprocal proportion between two numerical quantities.

VI. Valid Average and Valid Range

The mean, the median, the mode, and the range give only general information about the distribution of the observations; they fail to disclose the degree of spread or scatter of the data which, when too wide, invalidates the average. The establishment of a valid average is an essential step in experimental research to enable comparisons among different series of observations. To determine the validity of an average and of a range, an index called Standard Deviation must be used.

1. *Standard Deviation* (S.D.). The Standard Deviation is calculated as follows:

a. In the first left-hand column, list the data.

BASIC STATISTICAL CONCEPTS*

A. VALID COMPARISON:
   a. Alternate Allocation
   b. Frequency Distribution
B. MEAN, MEDIAN, MODE, AND STANDARD DEVIATION (S.D.)
   S.D. = SQ. R. of Average of Squared Deviations
C. VALID AVERAGE AND VALID RANGE (V.R.)
   V.R. = Mean + and — 2(S.D.)
D. STANDARD ERROR (S.E.) OR VARIATION DUE TO CHANCE
   S.E. = S.D. Divided by S.Q. R. of No. of Observations
E. SIGNIFICANT DIFFERENCE OR VARIATION GREATER THAN EXPECTED BY CHANCE
   Any Value Equal to Or Greater Than 2(S.E.)

EXAMPLES OF CALCULATION OF VALID AVERAGE AND SIGNIFICANT DIFFERENCE

DRUG MG	DEVIATIONS FROM THE MEAN	SQUARES OF THE DEVIATIONS	RESULTS
10	−20	400	ARITHMETIC AVERAGE OR MEAN = 30†
20	−10	100	RANGE = 10 TO 50
30	0	0	VARIANCE = MEAN OF SQ OF DEV'S = 1,000 ÷ 5 = 200
40	+10	100	STANDARD DEVIATION = SQ. R. OF 200 = 14.14‡
50	+20	400	VALID RANGE = 1.72 TO 58.28 30 − (2 x 14.14) = 1.72 30 + (2 x 14.14) = 58.28
			STANDARD ERROR = 14.14 ÷ $\sqrt{5}$ = $\frac{14.14}{2.2}$ = 6.5
			SIGNIFICANT DIFFERENCE = or > 2 x 6.5

* For discussion of these concepts, see text.
† This is a valid average because the lower and upper limits of the range (10 and 50) are respectively greater and smaller than the limits found as indicative of the valid range in this example (1.72 to 58.28).
‡ Standard Deviations greater than 20 are preliminary indications that the observations are widely scattered making their mean proportionately less valid.

Figure 6. Basic statistical concepts and examples of calculation of valid averages and significant difference

b. In the next column, list for each observation its deviation from the mean.

c. In the third column, list the square of the deviations.

d. From the third column, calculate the mean of the squared deviations. This is called the Variance.

e. Find the square root (Sq. R.) of the Variance; this is the Standard Deviation (S.D.). Thus, S.D. equals Sq. R. of Variance. Barlow's classic book[14] on squares, cubes, square roots, etc., makes it possible for even the non-mathematically trained worker to find the Standard Deviation and the Standard Error (to be mentioned below) of all numbers from 1 to 12,500.

The larger the value of the S.D. the less homogeneous the sample and the less dependable the results.

2. *Valid Average.* A valid average is considered that average which, when added to and subtracted from a value double the Standard Deviation, gives figures respectively higher and lower than the upper and lower limits of the range of the series used. The valid average, therefore, is representative of all the individual observations of the series.

In the example in Figure 6, 30 is a valid average because when added to or subtracted from 2 x (S.D. equals 14.14) it gives the values of 58.14 and 1.72, respectively, higher and lower than 50 and 10, the upper and lower limits of the range of observations in this example.

3. *Valid Range.* A valid range is considered any series of observations whose arithmetic average is a valid one. Thus, valid range equals Mean plus and minus 2 (S.D.). In the example in Figure 6, the range 10 to 50 is to be considered a valid one, since it is included within the values 1.72 = [30—2 (14.14)] and 54.15 = [30 plus 2(14.14)].

VII. Standard Error and Significant Difference

To evaluate the significance of the results of a research project, one must use a statistical index called the Significant Difference. This is based on a quotient showing the minimal variation due to chance, called the Standard Error, and applicable to samples of at least 50 or 60 cases.

1. *Standard Error (S.E.)* The Standard Error is obtained by dividing the Standard Deviation by the square root of the number of observations in a sample. Thus, S.E.= S.D. divided by Sq. R. of No. of observations.

2. *Significant Difference* or *Significance.* The Significant Difference is the accepted statistical measure of variations due to chance. The effects due to chance (e.g., spontaneous recovery) are unlikely to differ more than plus or minus twice the Standard Error, therefore the Significant Difference is any value equal to or greater than twice the Standard Error.

The example in Figure 6 shows a Standard Error of 6.5. Therefore, the Significant

Difference in the example is represented by values equal to or greater than (plus or minus) 2 x 6.5.

The discussion of more advanced statistical concepts such as the Coefficients of Variation and of Correlation, and the Chi-Square test is beyond the limited scope of this paper.

Conclusions

The statistical method cannot be of assistance at the conclusion of experiments conducted without proper preliminary planning. A properly planned experiment must consider at its very outset the three following elements:

1. The way in which the results are to be recorded and tabulated.
2. The means of securing uniformity, if different workers are involved.
3. The advice of a medical statistician on the statistical aspect of the project.

In medical papers we come upon a host of expressions such as "significant improvement," "significant advantage," and "significant difference," without taking into consideration the variations due to chance as measured by the Standard Error.

When faced with more or less authoritative claims that one form of treatment gives better results than another, even though the evidence is slender, the moral dilemma of experimenting with patients becomes acute. One cannot treat human beings like laboratory animals, and to withhold from a patient, for experimental purposes, a form of treatment which may be likely to help him, is unfair—to say the least. Such procedure would become totally obsolete and unnecessary if the early studies on new forms of treatment were conducted with proper planning along the lines of the statistical method.[15]

To make a patient well temporarily is not enough. This may indeed sometimes spell a brief course of an episode of illness, only to be followed by numerous relapses and rehospitalizations.

The discovery of safe and permanent methods of prevention and cure of illness is the final goal of medical science. The ultimate proof for claims by research scientists of effectiveness, permanence and safety in prevention and cure of illness lies only in the statistical method of medical research.[16]

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Psychiatric "Pointers" for the General Practitioner and Internist Treating Psychosomatic Diseases

EDMUND BERGLER, M.D.

The most important single psychiatric fact that the G. P. and internist who treats psychosomatic diseases must know is that *there exists within the patient an unconscious wish to suffer, and that this unconscious desire counteracts his conscious wish to get well.* The unconscious longing for pain, or "psychic masochism," accounts for the "incomprehensible" duration of some diseases, for equally "incomprehensible" relapses and recurrences, for illogical and inexplicable attitudes such as the failure to follow the doctor's orders, the constant flight from physician to physician, the failure to pay medical bills, and the generally provocative behavior displayed by some patients.

Too much stress cannot be put on the totally unconscious nature of the "wish to suffer," as opposed to the recovery wish. Consciously, disease changes the patient—whatever his disguise—into a scared, complaining, sometimes whining child who wants help and reassurance. Unconsciously, the patient also becomes a scared, complaining, whining child—but with a plus. This "plus" comprises the unbelievable fact that he enjoys his suffering and wants to cling to it.

The objection is unavoidable: Assuming but not admitting that this is so, what can the G.P. and internist do? He cannot and should not "analyze" the patient. He cannot refer every patient to a psychiatrist. He cannot even mention his smattering of psychiatric knowledge to some patients lest they counter with the indignant question, "Do you think I'm crazy?" Why, then, bother the overburdened physician with "unusable fantasies"?

In defense of knowledge, let it be said that two quite powerful reasons justify informing the physician that the unconscious wish to suffer is at work in every patient.

First, there is no place in medicine for either therapeutic nihilism nor overoptimism. But the G.P. will find it difficult to maintain even reasonable, cautious optimism when the favorable results presumably foreseeable and certainly expected from treatment fail to materialize, when the impatient patient blames the physician, when dissatisfaction and disgust—on the part of the patient for the physician, on the part of the physician for the patient—permeate the atmosphere. But if the physician knows that in a specific case the unknown factor consists of an overdose of psychic masochism, unreachable by a G.P.'s treatment, it may help his own "mental hygiene."

Second, although there is agreement that the G.P. and internist should not analyze the patient, *nothing prevents the physician from cautiously letting the patient know that every disease unconsciously "mobilizes" a specific amount of psychic masochism.* He can also—optimistically—add that the nuisance value of the disease may absorb this wish to suffer. But if the dose remains unabsorbed, additional—parallel—psychotherapy with a psychiatrist is indicated.

Now, what is the purpose of a statement stressing unconscious self-damage? It may benefit the patient. It may save the G.P. a good many reproaches from the patient and his family. How so?

The patient-physician relationship is more complex than meets the eye—or appears upon the bill. Once more, unconsciously, the patient projects upon the chance figure of the physician something peculiar: his own repressed fantasy of his own infantile omnipotence. This fantasy comprises feelings and illusions harbored by every child; in it the child can do whatever he fancies because he is all-powerful and all-knowing. Having unconsciously shifted this fantasy on to the physician—projection implies exactly that—the patient suddenly sees his doctor as a man with X-ray eyes, an authority who is all-powerful and, more important, all-knowing and all-seeing. The physician who gives a general, though tangential "interpretation" concerning the "wish to suffer" (even if he does so with a smile and not too portentously) sets something in motion

within the patient: inner fear. Paradoxically, this inner fear can prevent for at least a time the full emergence of the patient's lurking masochistic propensities.

Why should this be so? Many clinical examples in psychotherapy prove the point. Not all types of psychotherapy work with "deep interpretations" of the "uncovering type." Many operate with superficial suggestions of the "covering type"; many with blame-shifting, either social or cultural, or with interpretations so superficial that the deeper, dynamically decisive layers remain untouched. Nevertheless, all these therapies may result in temporary "successes." Some naive and not-too-smart observers erroneously conclude from such feats that the experience and emotional capacity of the psychiatrist outweigh in therapeutic importance the theories he carries in his head and the cards, attesting his membership in scientific societies, which he carries in his wallet, and the diplomas with which he adorns his walls.

Notwithstanding appearances, miracles do not happen, at least not in psychiatry. Specific reasons explain these temporary pseudo-successes. They rest upon a mechanism for which I have suggested the name, "pseudo-success because of unconscious fear." This mechanism was first described by myself in 1942; I have since enlarged on that description in my books, *The Basic Neurosis* (1949) and *The Superego* (1952). What happens is that the patient projects his own repressed megalomania onto the therapist, after which the therapist—ignorant as he may be—ranks as "omniscient." As the patient now inwardly sees him, he possesses the uncanny ability to discover *all* of the patient's secrets. To avoid that feared danger, *the patient unconsciously proceeds to sacrifice and renounce less important symptoms for a time, in order to keep the basic neurotic structure intact. Superficially,* a "cure" seems effected. This cure turns out to be pseudo all over; in *deeper* neuroses it is only transitory.

There is a resemblance between this mechanism and the following situation: An employee is in the habit of stealing money from the cash register. His employer is entirely unaware of his pilfering. One morning the young man looks very pale. The boss wants to tease him about his extensive night life and remarks, "You look very pale to me." The guilty one misunderstands this harmless remark; his guilty conscience leads him to see in it an allusion to the discovery of his thefts. It is quite possible that on the basis of the wrong conclusion the young man stops stealing—for a couple of weeks.

To revert to the "therapeutic" situation in pseudo-successes: The alleged change makes for gratitude all around. The patient seemingly, is grateful to the physician for the "cure"; the physician, seemingly, is grateful to the patient for having provided confirmation of his power to heal. Unfortunately, the unconscious state of affairs is different. The patient is grateful for having been permitted to retain a part of his unconscious pleasures, while the physician is due for a deep disappointment—the patient's symptom will recur. If the patient has the "decency" to alter his symptoms, the therapist's ignorance and failure to connect facts will spare him even this disappointment: he will not realize that masochistic self-damage is a single tree with many branches.

Now, what happens so frequently and unintentionally in psychotherapy with the not-too-well trained or not-too-well informed psychiatrist (and admittedly this is a rather grotesque situation) can be seriously and intentionally put to use by the G.P. It is quite legitimate, I believe, for the internist and G.P. to apply as a palliative this not infrequent psychiatric error. The great mass of patients cannot afford psychiatric-psychoanalytic treatment. Aside from the question of cost, most of them are unwilling to seek it; if they were willing, there would not be enough trained psychiatrists available. Instead of shrugging one's shoulders and claiming the protection of the phrase, "Nothing can be done," one can advocate the stopgap technique outlined here. A famous novelist, the late Charles Yale Harrison, once said: "The stopgap became a way of living, which is how it is with stopgaps."

In suggesting this "stopgap technique," it should be made clear that its purpose is by no means that of supplanting psychiatric-psychoanalytic treatment, treatment that goes to the root of the neurotic problem with all its masochistic ramifications. Quite the

opposite: in severe cases, only analysis of the masochistic regression can help. But the "stopgap technique" has its place as a trial balloon. It is harmless and may help in some cases.

To use a clinical example: A G.P. treats a man with ulcer of the stomach. Medication, diet, avoidance of alcohol, etc., help overcome the most acute symptoms. But in some cases these masochistically perceived sacrifices—who doesn't like to eat and take a drink?—do not suffice. Psychoanalysis should then be recommended to follow, or even better, parallel the internist's treatment. The psychoanalyst will typically find that the patient is a classical "injustice collector" who unconsciously plays this "game": To reduce the image of the "bad, refusing" mother to absurdity, he denies the inner accusation that he masochistically wants to be refused by demonstrating the opposite, "I want to get." To "document" his alleged wish to get he produces generous amounts of gastric acid as the preparatory act of digestion. The process is comparable to the flow of saliva resulting from thoughts of one's favorite food. But the gastric acid thus produced finds no food upon which to work; instead it "eats up" the mucosa of the stomach. In extreme cases the process ends in a neat hole.

Obviously, in severe cases, medication and diet alone cannot change the psychic structure. If the patient does not possess the means or the relative lack of resistance to therapy that would permit him to enter psychiatric treatment, or if he lives in a community lacking trained psychiatrists, the "stopgap technique" can be applied. It is also recommended in not-too-severe case of neurotic personality structure.

The patient's personality structure, of course, supplies the cue to the entire problem. Let us clarify the fact that self-damage, the ominous unconscious "pleasure-in-displeasure" pattern, is universal. A "masochistometer," if it could be invented, would undoubtedly show that people who possess up to a 49% deposit of that infantile scourge are those euphemistically called "normal," whereas the "higher brackets"—those registering above 51%—comprise the "neurotics." Only a quantitative difference separates the two. And even this separation would be fallacious. The imaginary scale could register only the masochistic deposit of the moment, and the distribution of the inner scourge of masochism is by no means static. At specific times, the score may increase under the impetus of certain disappointments, frustrations, or the collapse of cherished aims which are in reality defenses.

Today, people in general concede and accept the existence of inner conflicts, but—as is usual with new things—their acceptance rests more on misconceptions than on understanding. The G.P. confronted with psychosomatic manifestations often asks whether some emotional upset preceded the disease. When he hears of conflicts, mostly consisting of "anger" or "tensions" or "disappointments,' he tends to jump to the conclusion that the patient suffers from "undischarged aggression' which has materialized against himself because of inner guilt. This is an everyday faulty diagnosis. Actually, what is visible at the high point of neurotic conflicts is never suppressed or repressed aggression, but psychic masochism covered by a thin layer of defensive fake aggression, scientifically designated as "pseudo-aggression." The reason is simple. Nobody wants to admit, even to himself, to being a masochist. Anger and aggression, however, have the consoling connotation of being acceptable to the conscious ego; they are understandable, heroic and what not. Anyone who believes that repressed real aggression contributes to neurotic conflicts is as naive as the detective who follows the clues planted by the wrongdoer.

"Pseudo-aggression," covering psychic masochism, never fails to manifest itself in the behavior of the patient towards the physician. "Transference"—the repetition of repressed infantile conflicts in situations involving innocent outsiders—is not a prerogative of the analytic situation. It occurs on and off the analytic couch. The analyst, of course, uses it productively in dynamic interpretations. When transference occurs away from the analytic couch, no productive use follows; the outsider merely remains the victim of the repetition. When the repetition involves physician and patient, the G.P. should not be deceived by the patient's display of childlike helplessness and fright.

Consciously, to be sure, the patient wants sympathy, understanding and help. But unconsciously he wants suffering, and uses defensive aggression. This explains the double attitude of trust and mistrust, submission and rebellion, towards the objective helpful physician.

This two-faced view of the physician also explains one of the least explored and paradoxical of attitudes found in patients: the reluctance to pay medical bills. "Reluctance," it goes without saying, is a polite understatement. Patients explain their delinquency with a wealth of silly rationalizations, such as "A physician should be ashamed to think about money" or "Health is something so precious it should not be measured in money." Under these rationalizations lie two unconscious facts.

First: As far back as the patient can remember, his parents were the people who concerned themselves with his health. When, as an adult, he consults a physician who must be paid for his services, all his infantile resentment against "not being loved" enters the picture. Whoever heard of parents asking for money from their child when the child is sick? Once more, masochistic "injustice collecting" comes to the fore in the infantile adult.

Second: The projection of the patient's own infantile megalomania upon the chance figure of the physician has already been stressed. Here a basic difference between the physician and every other human being enters the picture. The physician alone, in his medical sphere, seems to have escaped the general fate of humankind; he, uniquely, has not had to relinquish that megalomania. He has some connection with this magic of infancy. His close link with life and death makes him—unconsciously—a bearer of magical powers. Hence, the reluctance to pay medical bills also has connections with emotional objections against one who still is clothed in the old but never outworn fantasy of childlike megalomania. The patient who puts off and puts off paying a medical bill is postponing what he unconsciously sees as a contribution to the support of a competitor who remained in the business while he himself was forced out of it.

There is only one exception to this form of behavior, and even then magic again plays a part. Strangely enough, these are patients who are overly prompt in paying medical bills. In most cases they do so because they are afraid of the doctor's magic power of revenge. They pay quickly in an unconscious attempt at appeasement, and in the unconscious hope that they can thus prevent his magical wrath. This is, by the way, the reason why physicians, and physicians alone, have achieved the unachievable: they cannot be openly shouted at. Nobody hesitates to shout at an engineer, an architect, lawyer, manufacturer or even atomic scientist, but there exists the tacit agreement that shouting is entirely unacceptable in the patient-physician relationship.

Many questions of psychosomatics cannot be entered upon here because of space limitations; these include the meaning of "tensions," more recent evaluations of the role of sex life in the psychic economy, etc. One topic, however, can be covered briefly; it rates its priority because of its frequency and because of the widespread misunderstanding connected with it. This is the matter of psychosomatic diseases linked with man's "middle age revolt." Although a good deal has been written about woman's climacteric complaints, little or nothing appears in the medical literature on man's difficulties in the late forties and middle fifties. Without discussing whether or not there exists a physiological substratum, I would like to stress the fact that every man goes through a period of crisis at some time during these decades. The "revolt" is not always full-fledged; sometimes it is abortive. It could be summed up as the stage when the man realizes that his youth has passed, and his inner conscience sits in judgment over hopes that have not materialized, illusions that have shattered, successes that have eluded the man's grasp. In other words, it is a masochistic field day. The battered ego fights back by attempting to achieve the irretrievably lost—and to do so in a hurry. Preceding this comes a phase in which the familiar becomes stale: office, work, social circle, hobbies, and especially the wife. She becomes the prime malefactor who holds the middle-aged man down. He thinks of di-

vorce and a new start, of life begun again with a younger woman. This "middle age revolt" is thus but an "emotional second adolescence" as I pointed out in my book "Revolt of the Middle Aged Man," 1946.

Most of the time, these "psychic measles" are harmless and the revolt collapses: masochism wins out. But one specific group of middle-aged pseudo-rebels retires into psychosomatic diseases or hypochondria, in order to provide themselves with an inner excuse for abandoning their grandiose plans. These people are beyond medical treatment so long as the core—namely, the abortive "middle age revolt"—remains unclarified. Actually, no treatment dispensed by an internist can have any effect upon personalities of that age group with a leaning towards hypochondria. The reason becomes clear if one thinks about the masochistic basis of the disease. Hypochondriacs elevate specific organs to the position of a self-appointed dictator; this leaves them self-appointed serfs. Masochism provides the cement which leaves this pattern impervious to any except psychiatric treatment.

To sum up: Among the many psychological complexities which face the G.P. and internist when treating patients with psychosomatic illnesses, one has been singled out for special consideration. This is the patient's hidden wish to suffer. The ancient Roman philosopher and dramatist Lucius Annaeus Seneca (5-65 A.D.) stated: "It is a part of the cure to wish to be cured." This conscious "wish to be cured" is impeded by the opposite unconscious tendency: the wish to suffer and continue to suffer. Since the G.P. cannot send every patient addicted to suffering into psychiatric treatment, the suggestion is made that he institute an automatic inner reaction in the patient, a reaction that will work in the direction of relinquishing symptoms. In a form of "stopgap technique," the physician would make the patient aware of the presence of these masochistic, self-defeating deposits. Although no physician can do what a wit described, "Some people think that doctors can put scrambled eggs back into the shell," he can help. All of today's progress in medicine can be judged when we compare the contemporary physician's admittedly still imperfect knowledge with Oliver Wendell Holmes' judgment of his own profession almost one hundred years ago. In an address delivered before the Massachusetts Medical Society on May 30, 1860, this leading physician declared: "I firmly believe that if the whole materia medica as now used could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes." Today, perhaps, Holmes would retract this statement, and not wish all the good things on the fishes.

An old G.P. of my acquaintance complained about the endless succession of "fads" he had encountered throughout his lifetime, and bitterly recounted examples of "unlearning" he had been forced into by his patients, propelled in their turn by newspaper reports. He was especially indignant about the newest "unlearning" imposed upon him—psychosomatics. "Life is just one damn thing after another," he quoted. I consoled him by reminding him of the principle of shared responsibility. In the past, every uncured case meant an offense to his fantasy of medical omnipotence. Today the G.P. can shrug his shoulders and gloatingly say, "It's a case for the psychiatrist."

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Vocational Rehabilitation as a Therapeutic Tool

JOHN T. TOPPEN, M.D., and HARVEY E. WOLFE, M. ED.

The average hospital for the mentally ill has potential resources for the development of a good vocational rehabilitation program for its patients. The long periods required for treatment and convalescence in severe psychiatric illness often result in loss of former skills through disuse. In addition, many patients will have had no vocational skills and may have been able to support themselves at only marginal levels, if at all, before they entered the hospital. The patient and staff are, therefore, often confronted with the prospect of demoralizing economic dependency of the patient, even after he is clinically improved or recovered. This problem is made worse by the reluctance of employers to accept previously institutionalized people. An in-hospital program designed to anticipate and meet this problem can consequently add much to the "therapeutic community" by restoring the patients' morale, equipping him for independence, and fortifying him against recurrences of illness by way of its ego-strengthening effects.

An important consideration, however, is that to be truly useful, vocational rehabilitation must be a continuous, meaningful process for the patient, hospital staff and community agencies working with the hospital. Vocational rehabilitation should consist of all of the following services: vocational, physical and psychiatric evaluation, counselling, education or training, selective hospital or outside job placement, and follow-up.

In the hospital, when the patient is judged psychiatrically ready for it, an assignment to work therapy should be made. The assignment should be consistent with the clinical and test findings and also take into consideration the patient's past work experience, interest, and educational attainments. The work therapy assignment, in addition to its psychiatric implications, provides a useful means for vocational diagnosis and work evaluation of the patient.

From Longview State Hospital, Cincinnati, Ohio.

With the help of the various supervisors, the patient's level of development in work and on-the-job social skills should be carefully observed and reported through written and oral reports. This information is presented to the medical staff and a cumulative record is kept on each patient by the Vocational Rehabilitation Department.

The patient's work tolerance, or total ability to work in a competitive setting, is evaluated as are many other factors such as job attendance, cooperation, sociability—both with other patients and employees, general work behavior or deportment and the quality of work performance.

The patient's work progress should assist the ward physician in determining his readiness for training and/or outside employment. Regular evaluation of each patient pinpoints his progress and makes possible an individualized approach to his rehabilitation. The work therapy program makes possible the use of real work settings instead of the unrealistic, make-work situations too often found in outside rehabilitation centers. It also makes possible the use of the "team" approach, making use of the many disciplines found under one roof in the hospital. Psychiatrists, occupational therapists, vocational counselors, social workers, psychologists, nurses and attendants all play a vital role in the rehabilitation of the patient. The very significant role of the attendant has all too often been over-looked, but now he is taking an increasingly important place as a member of the therapeutic team. In addition to work therapy the patient should have a balanced individualized program of activities such as organized recreation, music therapy, group work, special prescription occupational therapy, and so forth.

The Occupational Therapy Department can be of assistance in prevocational diagnosis of many patients as well as in assisting with the improvement of the activities of daily living, especially with the brain-damaged group. With this group a prescription program of psychological retraining can often be of value.

As the patient's readiness and will for reintegration into the community approaches, counselling, and in some cases special testing, should be done as well as a reappraisal of his entire record to help determine whether further training is indicated, or possibly a direct outside work placement. If training is indicated, on-the-job training can be set up within the hospital in such work areas as hospital supply, beauty shop, laundry, shoe repair, carpentry, plumbing, painting or various other trade jobs at the helper level. Arrangements can also be made for elementary or high school equivalency examinations where there is aptitude and interest. When very special training not available in the hospital, seems indicated, the State Bureau of Vocational Rehabilitation is called in and becomes part of the team for these patients, carrying responsibility for them through training and placement. Supportive hospital resources such as psychiatric casework should be made available on a continuing basis. The majority of patients have as their chief need, selective job placement and psychiatric casework follow-up.

After an employment objective has been determined the patients needing help in attaining it are referred to the Vocational Placement Service, which operates very much like commercial employment services. The placement service at Longview State Hospital is currently operated, under close supervision, by trained volunteers because of the shortage of hospital personnel. All the modern employment techniques are used in the service which constitutes a very effective approach to the employment problem, from the standpoint of placement as well as of community education.

There is a large residual group unemployable because of age (at Longview State Hospital, approximately 30% of the daily census is 65 years and older). A psychiatrically oriented, sheltered workshop is badly needed by many of this group and since many have the additional problem of no home to return to, it would seem that this shop should be part of the hospital facilities.

Another group will remain unemployable because of psychotic residuals, character disturbances, convulsive disorders, and so forth. At the present time a limited number from this group is being filtered into the work adjustment center for emotionally disturbed, operated by Jewish Vocational Services. This facility is a pilot project and a prototype of the Gellman Project at Jewish Vocational Services in Chicago. It is hoped that new avenues will be developed for working with this unemployable group.

There is a great need for continuing research into all possible approaches to the vocational rehabilitation of the mentally ill. It is to be hoped that more data will be accumulated for use in refinement of such programs.

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Combinet Effects of Chlorpromazine and Meprobamate in Chronically Disturbed Psychotic Patients

JOHN C. POLLARD, M.D., B.S.

Purpose of Study:

The mode of action of the psychopharmaceuticals is still largely not understood. Therefore, administration is often on an empirical basis. If one compound fails to produce improvement it is reasonable to try another, or indeed a combination of two or several. Barsa and Kline,[1] have noted that chlorpromazine and meprobamate combinations merit study. This is the purpose of this assay, particularly inasmuch as chlorpromazine alone had failed to produce behavioral change in the patients tested.

Selection of Patients:

The patients were selected from the 320 in the disturbed women's building of a state hospital (Warren State Hospital, Warren, Pennsylvania): 22 were selected that fulfilled the following requirements.

(1) They were chronic psychotic patients with a duration of illness of at least 24 months—12 of which had been spent in the hospital. Record of behavior during this time had shown that each patient had never gone through a six-week period without becoming so disturbed that either electroshock therapy, seclusion, or a cold wet sheet pack was necessary. Thus a disturbed period during the evaluation time would be expected. All had had EST.

(2) They had all been considered chlorpromazine failures—inasmuch as behavior had not been significantly altered by this drug alone. Failure was only considered after the patient had received chlorpromazine for at least three months and had received a minimum of 200 mgms. daily for two months. The majority had had more (see Tables).

(3) All patients had been on chlorpromazine for three months prior to onset of test and during the test period were continued on the dose they had received for the previous two months.

From Mental Health Research Institute University of Michigan, Ann Arbor, Michigan.

TABLE 1

Combined Medication

Diagnosis		Age	Dosage mgms./day Chlorpromazine	14 days after	40 days after	68 days after	14 days after
Sc.u.		18	300	2	1	0	0
Psy.		73	400	2	2	1	1
Sc.p.	EST	29	300	0	1	0	0
Sc.p.	EST	38	400	0	2	2	1
Sc.p.	EST	28	450	1	1	1	1
Sc.u.	EST	41	300	1	0	0	0
Sc.p.		48	600	2	2	D	EST
Sc.u.		34	400	1	0	0	0
Psy.		35	200	0	0	1	1
Sc.s.		43	250	2	0	D	EST
Sc.u.	EST	39	400	1	1	1	0
Sc.s.		50	400	0	0	0	0

Only two out of 12 patients did not complete the course.

Placebo and Chlorpromazine

Sc.h.		40	300	0	D	EST	
Psy.		23	200	0	0	D	EST
Psy.		26	450	0	0	0	0
Sc.		29	450	0	1	1	0
Sc.h.		38	600	0	0	D	EST
Sc.p.		30	300	0	0	0	0
Sc.p.		35	600	0	0	0	0
Sc.p.		36	250	0	0	0	0
Sc.h.	EST	44	450	1	1	1	1
Sc.p.		43	800	0	0	0	0

Three out of 10 patients did not complete course. They became very disturbed and EST was given.

Sc.=schizophrenia
u=undifferentiated
s=simple
c=catatonic
h=hebephrenic
p=paranoid
Psy.—Psychosis unclassified
EST—Patient previously on electro-shock therapy once weekly
D, EST—Drug discontinued. EST given.
0=no change
1=some improvement
2=marked improvement
Dosage Meprobamate: 4800 mgms. daily. Report 14th day.
4800 mgms. daily. Report 40th day.
9600 mgms. daily. Report 68th day.
Report 14th day.

The tables show the diagnostic cateogry, age, length of time in hospital and chlorpromazine dosage in mgms. and total length of drug therapy prior to test. In the test group all patients were psychotic, the range of ages from 18 to 73 years, average 39.7 years. Hospitalization ranged from 1.5 to 28 years, average 10.9 years. The average chlorpromazine dosage was 366.6 mgms. daily for 7.6 months.

In the control group all patients were psychotic, ages ranged from 23 to 44, average 34.4 years, hospitalization was from four to 14 years, average 8.6 years. Chlorpromazine dosage was 440 mgms. daily for 8.1 months.

The meprobamate dosage during the study was 4800 mgms. (three 400 mgms. tablets four times daily) for 40 days and then the dose was doubled. For the first three days of the study the subjects received only one tablet—400 mgms. daily in case of any drug idiosyncrasies or adverse effects. None was noted.

Evaluation of Behavior Reports:

The rating was entirely made on the evaluation of behavior: the patients were chronically disturbed psychotics—some being entirely non-communicative verbally and so it was a practical expediency that all were evaluated in the same areas of behavior, not just by interview. The physician was the only person who interviewed the patients during the period of selection and, as he alone knew which medication was being received by whom, no further deliberate contact was made by him with these patients. The staff of registered nurses, all experienced psychiatric nurses, made the rating in the following areas:

1. Self care.
2. Cooperation.
3. Communication.
4. Socialization.
5. Special observations.

Summary of Results:

After 14 days there was an observed improvement in eight of the 12 on meprobamate and chlorpromazine. Two were considered to be remarkably improved. During the same period two of the 10 on placebos and chlorpromazine were also considered improved.

After 26 days later seven of the patients on meprobamate and chlorpromazine were still considered improved, but two of these seven were not in the first improved group: therefore three patients had relapsed. The increase in medication brought little change —but by the time drug withdrawal was complete five patients were considered to still be showing behavioral improvement. Two weeks after cessation of the drugs only one of the five had relapsed.

In the meprobamate and chlorpromazine group four patients were on "maintenance shock" once weekly: although two of these were not in the improved group they did not require EST throughout the 10-week test period. Two other patients, both considered initially improved did become acutely disturbed during the third phase and required EST.

In the placebo group there were two "maintenance shock" patients. One required EST after two weeks, the other patient throughout the test period improved so remarkably that the observers were "convinced" she was on the medication. Her improvement on placebo therapy not only obviated the need for shock but brought laudatory comments from the relatives. (There are, of course, many possible explanations of a non-pharmacological nature for this improvement.) No other patients on the placebo maintained a significant change.

Other Features Noted: Bed-wetting. One patient, was regularly enuretic. During the entire period of test she was not troubled this way, but on cessation reverted to the unfortunate habit.

The patient that showed the most remarkable over-all change was a chronic catatonic schizophrenic. Negativistic, withdrawn and usually mute, after three weeks of combined therapy she spoke more readily, cooperated and made timid gestures of interest in her surroundings that she had not shown for 15 years. Her mother took her home on visiting days and related that her daughter had conversed with her in a way she had scarcely been able to recall. This

improvement was maintained two weeks after cessation of the drug.

Side Effects: Except for a drowsiness for the first few days there were no side effects whatsoever: when the drug was increased in the third phase, there was no marked drowsiness as there had been at the onset. There were no dermatoses or other allergic phenomena. Regular blood work showed no abnormalities.

There were no side-effects in the placebo group.

Withdrawal: The drug was withdrawn over seven days during which time no adverse reactions were noted. Weight changes were not significant.

Summary:

Twelve patients, all chronic, disturbed psychotic women were tested with meprobamate and chlorpromazine combination.

Chlorpromazine had shown no marked change in behavior.

A control group of 10 were given chlorpromazine and a placebo. Eight of the 12 patients on combined drugs improved during the first two weeks, but only five were still improved seven weeks later. The early improvement of eight out of 12 is highly significant, even though factors other than the drugs may be at work at this early stage. Reversion to former difficulties may suggest a tolerance, but a sizeable increase in dosage made little difference. Two patients of the control group improved—but one only maintained this improvement throughout the test period.

It is apparent from these studies that meprobamate with chlorpromazine in combination has an ameliorating effect on behavior in chronic psychotic patients.

It is suggested that this study be repeated with acute psychotic patients, making both objective and psychometric evaluations.

Acknowledgment: Equanil and placebo supplied by Wyeth Co.

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